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The Dean and Betty Gallo Prostate Cancer Center
The Cancer Institute of New Jersey
Department of Defense
Annual Report
July 1, 2003 - June 30, 2004

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Abstract

The Dean and Betty Gallo Prostate Cancer Center (GPCC) was established with the goal of eradicating prostate cancer and improving the lives of men at risk for the disease through research, treatment, education and prevention. GPCC was founded in the memory of Dean Gallo, a beloved New Jersey Congressman who died tragically of prostate cancer diagnosed at an advanced stage. GPCC unites a team of outstanding researchers and clinicians who are committed to high-quality basic research, translation of innovative research to the clinic, exceptional patient care, and improving public education and awareness of prostate cancer. GPCC is a center of excellence of The Cancer Institute of New Jersey, which is the only NCI-designated comprehensive cancer center in the state. GPCC efforts are now integrated well as part of our Prostate Program at CINJ, in which Dr. Robert DiPaola and Dr. Cory Abate-Shen are co-leaders.

The Prostate Program unites 19 investigators from 10 academic departments who have broad and complementary expertise in prostate cancer research. The overall goal and unifying theme is to elucidate basic mechanisms of prostate growth and oncogenesis, with the ultimate goal of promoting new and effective strategies for the eradication of prostate cancer. Members' wide range of research interests collectively optimize the chances of providing new insights into normal prostate biology and unraveling the molecular pathophysiology of prostate cancer. Cell culture and powerful animal models developed by program members recapitulate the various stages of prostate cancer progression, including prostatic intraepithelial neoplasia, adenocarcinoma, androgen-independence, invasion and metastases. These models promise to further strengthen an already robust program of investigator-initiated therapeutic clinical trials, including studies adopted by national cooperative groups. Efforts to translate laboratory results into clinical studies of early detection and chemoprevention are underway.

The specific goals of this program are:

1. To investigate the molecular mechanisms underlying normal prostate growth and differentiation and elucidate the molecular mechanisms underlying prostate oncogenesis.
2. To build on fundamental knowledge to develop effective therapeutic approaches for the treatment of prostate cancer.
3. To improve the control of prostate cancer through early detection, chemoprevention, and outreach and education.

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This new disease-based program is structured to improve interdisciplinary interactions and translational results. Already, through the dynamic leadership of Drs. Cory Abate-Shen and Robert DiPaola, new investigators were attracted to the field, new collaborations engendered, and numerous investigator-initiated trials implemented.

Progress in GPCC and the program overall has been outstanding. The Center has success in uniting investigators with broad and complementary expertise in prostate cancer research. The overall goal and unifying theme is to elucidate basic mechanisms of prostate growth and oncogenesis, with the ultimate goal of promoting new and effective strategies for the eradication of prostate cancer in patients and populations at risk. Members' wide range of research interests collectively optimize the chances of providing new insights into normal prostate biology and unraveling the molecular pathophysiology of prostate cancer. Studies in cell culture and powerful animal models developed recapitulate the various stages of prostate

cancer progression, including prostatic intraepithelial neoplasia, adenocarcinoma, androgen-independence, invasion and metastases. These models promise to further strengthen an already robust program of investigator-initiated therapeutic clinical trials, including studies adopted by national cooperative groups. Efforts to translate laboratory results into clinical studies of early detection and chemoprevention are underway.

PROSTATE CANCER PROGRAM
DOD Annual Report
Program Co-Leader: Cory Abate-Shen, Ph.D.
Program Co-Leader: Robert DiPaola, M.D.

Program Members

Investigator	Department
Cory Abate-Shen, Ph.D.	Neuroscience and Cell Biology (RWJMS)
Paul Copeland, Ph.D.	Molecular Genetics, Microbiology and Immunology (RWJMS)
Steven DiBiase, M.D.	Radiation Oncology (RWJMS)
Robert DiPaola, M.D.	Medicine (RWJMS)
Joseph Fondell, Ph.D.	Physiology and Biophysics (RWJMS)
Ramsey Foty, Ph.D.	Surgery (RWJMS)
William N. Hait, M.D., Ph.D.	Medicine and Pharmacology (RWJMS)
Diane Heck, Ph.D.	Pharmacology and Toxicology (RU)
Longqin Hu, Ph.D.	Pharmaceutical Chemistry (RU)
Jeffrey Laskin, Ph.D.	Environmental and Community Medicine (RWJMS)
Grace Lu-Yao, Ph.D.	Environmental and Community Medicine (RWJMS)
Ronald Morton, Jr., M.D.	Surgery (RWJMS)
John Pintar, Ph.D.	Neuroscience and Cell Biology (RWJMS)
Arnold B. Rabson, M.D.	Molecular Genetics, Microbiology and Immunology (RWJMS)
Danny Reinberg, Ph.D.	Biochemistry (RWJMS)
Monica Roth, Ph.D.	Biochemistry (RWJMS)
Armen Sarvazyan, Ph.D.	Surgery (RWJMS)
Michael Shen, Ph.D.	Pediatrics (RWJMS)
Mark Stein, M.D.	Medicine (RWJMS)
Mary B. Todd, D.O.	Medicine (RWJMS)
Robert Weiss, M.D.	Surgery (RWJMS)

Scientific Goals

GPCC and the program overall has success in uniting investigators with broad and complementary espertise in prostate cancer research. The Prostate Program unites investigators with broad but complementary expertise in prostate cancer research. The overall goal and unifying theme is to elucidate basic mechanisms of prostate development and oncogenesis, with the ultimate goal of promoting new and effective strategies for the eradication of prostate cancer. Members have a wide range of research interests that collectively optimize the chances of providing new insights into normal prostate biology, as well as unraveling the molecular pathophysiology of prostate cancer. Studies in cell culture systems and animal models recapitulate the various stages of prostate cancer progression, including prostatic intraepithelial neoplasia, adenocarcinoma, androgen-independence, invasion and metastases. These models promise to strengthen the already robust menu of investigator-initiated therapeutic and preventive clinical trials, including studies adopted by national cooperative group. Efforts to tranlate laboratory results into clinical studies of early detection and chemoprevention are underway.

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PROGRAM CO-LEADERS:¶
Cory Abate-Shen, Ph.D.and Robert DiPaola, M.D.¶
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1. To investigate the molecular mechanisms underlying normal prostate growth and differentiation and elucidate the molecular mechanisms leading to prostate cancer.
2. To build on fundamental knowledge to develop effective therapeutic approaches for the treatment of prostate cancer.
3. To improve the control of prostate cancer through early detection, chemoprevention, outreach and education.

Scientific Accomplishments

Members of the Prostate Program made important contributions in each of the main focus areas. These accomplishments are summarized below.

1. To investigate the molecular mechanisms underlying normal prostate growth and differentiation and elucidate the molecular mechanisms leading to prostate cancer.

RATIONALE/CANCER FOCUS: Through a fundamental understanding of prostate biology gleaned from a combination of *in vivo* and *in vitro* approaches, program members are making important inroads into understanding the pathways of prostate cancer initiation and progression. One of the principal accomplishments of the Prostate Program is the generation of new mouse models of prostate cancer. These models stimulated a broad range of multidisciplinary studies on the mechanisms of prostate cancer development, the elucidation of molecular events associated with disease progression, and have the potential for developing new paradigms for prevention and treatment. Summarized below are examples of these research accomplishments.

ACCOMPLISHMENTS: The collaborative efforts of Cory Abate-Shen and Michael Shen elucidated a critical role for the *Nkx3.1* homeobox gene in the development of the normal prostate and how defects in its expression contribute to the development of prostate cancer. GPCC has supported the development of the transgenic mouse core facility at CINJ. They demonstrated that *Nkx3.1* is the earliest known marker of prostate formation and that it is required for appropriate prostate morphogenesis and epithelial differentiation. These studies were accelerated by their creation of mutant mice with loss-of-function of *Nkx3.1*. Using transcriptional profiling of normal and mutant mouse tissues, they are uncovering the mechanisms by which *Nkx3.1* regulates prostatic epithelial differentiation. For example, they found that *Nkx3.1* mutants express genes that are usually restricted to seminal vesicles, suggesting that loss-of-function of *Nkx3.1* leads to defects in prostatic epithelial specification. They hypothesized that these defects in specification predispose *Nkx3.1* mutant mice to malignant transformation of the prostate. These studies provide important insights linking the control of differentiation to mechanisms underlying oncogenesis, as well as the role of homeobox genes in these processes (Abate-Shen, *Nat Rev Cancer*, 2002; Abate-Shen, *Cancer Cell*, 2003; Shen and Abate-Shen, *Dev Dyn*, 2003).

Shen applied his expertise in vertebrate development using mouse models (Ding et al., *Nature*, 1998; Yan et al., *Genes Dev*, 1999; Schier and Shen, *Nature*, 2000; Iratni et al., *Science*, 2002; Morkel et al., *Development*, 2003; Shen, *J Clin Invest*, 2003) to the study of prostate biology (Bhatia-Gaur et al., *Genes Dev*, 1999). He generated mice carrying an *Nkx3.1-lacZ* knock-in allele, which enabled him to develop a novel explant culture system that supports the reproducible growth and differentiation of prostatic epithelium *in vitro* (*Dev. Bio.*, 2003, in press). Dr. Shen and colleagues used this assay to quantify the formation of prostatic ducts in explant cultures using embryonic tissues that normally give rise to prostate from wild-type and mutant mice. This assay can be adapted for rapid screening of therapeutics agents that affect prostatic growth. In collaboration with Dr. Philip Beachy's laboratory at John's Hopkins, they found

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Deleted: 3. Cancer Focus/Rationale¶ ¶ Prostate cancer is the most common non-cutaneous malignancy afflicting men in the United States. Furthermore, for reasons that remain uncertain, this form of cancer has a peculiar predilection for African Americans. Since the incidence of prostate cancer increases with age, the significance of prostate cancer will continue to increase aging is an important risk factor for prostate cancer, as Americans enjoy longer lives, the significance of prostate cancer will continue to increase. The availability of Asensitives effective methods of for screening have become available, theincreased the frequency of diagnoses has transiently increased, leading to an explosion of utilization of surgical, radiation, and systemic treatments. Coupled with the discovery of many new systemic agentspotential new drug targets, the need for interactions between laboratory, clinical and population researchers and a multidisciplinary clinical research team to develop agents earlier in disease has never been more pressing. Furthermore, as a higher percentage of population gets older and thereby more susceptible to prostate cancer, there is a greater need for new strategies for prevention. Thus, the rationale for the development of this new CINJ program is to establish a multidisciplinary team of researchers with diverse scientific expertise ... [12]
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that inhibition of sonic hedgehog (Shh) signaling had adverse consequences for prostate morphogenesis. Their studies also demonstrated that defects in prostate morphogenesis in *Shh* mutants is an indirect consequence of a partial deficiency in androgen production; *Shh* does not appear to be essential for prostate induction, but is required for prostate morphogenesis. Given the importance of aberrant Shh signaling in other cancers, these findings suggest a role for this signaling pathway in the genesis of prostate cancer.

Signaling through the insulin-like growth factor (IGF) pathway became an entry point for John Pintar into prostate cancer research. Pintar investigates the role of IGF binding proteins (IGF-BPs) in normal growth and development using mutant mouse models generated in his laboratory (Pintar et al., *Prog Growth Factor Res*, 1995; Pintar et al., *Horm Res*, 1996; Grewal et al., *Horm Metab Res*, 1999; Wood et al., *Mol Endocrinol*, 2000; Nitsche et al., *J Neurosci*, 2002; Clarke et al., *Neuroscience*, 2003; Nitsche and Pintar, *Dev Biol*, 2003). Inspired by work of others, who had shown that serum levels of IGF were linked to prostate cancer risk in humans, he applied for and received funding from CINJ Developmental Funds to explore the consequences of loss-of-function of IGF-BPs in prostate cancer. He found that IGF-BP mutant mice displayed hyperplasia and dysplasia of the prostate that was consistent with a pre-cancerous phenotype. He is now investigating whether this phenotype can be exacerbated by combinatorial mating with prostate-cancer-prone strains, such as *p53*, *Pten*, and *Nkx3.1*, through collaborations with Abate-Shen and other program members.

Understanding androgen-mediated signal transduction is essential to our knowledge of basic prostate biology and to the pathophysiology of prostate cancer. Joseph Fondell was newly recruited to the faculty and to the field of prostate cancer research to apply his expertise on androgen receptor (AR) physiology to the study of prostate cancer. His laboratory developed a unique series of cell lines that express an epitope-tagged AR to isolate interacting proteins that are likely to regulate transcriptional activity (Wang and Fondell, *Anal Biochem*, 2001; Sharma and Fondell, *Proc Natl Acad Sci U S A*, 2002; Zhang et al., *Oncogene*, 2002). Dr. Fondell demonstrated that AR interacts with the TRAP/Mediator protein, which was first identified as a transcriptional co-activator for another nuclear hormone transcription factor (Sharma and Fondell, *Proc Natl Acad Sci U S A*, 2002). Using chromatin immunoprecipitation assays to define interactions with chromatin templates in cell culture, he found that components of the TRAP complex interact with AR on androgen-responsive promoters in LNCAP prostate cancer cells. Fondell is testing the hypothesis that one of the mechanisms underlying the transition from androgen-dependence to androgen-independence in prostate cancer involves the potential of AR to associate with distinct protein complexes in androgen-responsive versus non-responsive cells. He is collaborating with Danny Reinberg to investigate chromatin assembly in prostate cancer, and with Shen to develop mice having epitope-tagged versions of AR to investigate AR-associated proteins *in vivo* as a function of prostate cancer progression.

Reinberg, an international leader in the field of transcriptional regulation, recently embarked on prostate cancer research through his interest in factors that alter chromatin structure and regulate gene expression (Kuzmichev et al., *Genes Dev*, 2002; Nishioka et al., *Genes Dev*, 2002; Nishioka et al., *Mol Cell*, 2002; Belotserkovskaya et al., *Science*, 2003; Friedl et al., *Proc Natl Acad Sci U S A*, 2003; Saunders et al., *Science*, 2003). His laboratory isolated PRC2 from HeLa cells and found that it methylated lysine-27 on the histone H3 tail. They found that the enzymatic activity of PRC2 resides in a polypeptide termed Enhancer of Zeste (Ezh2). Ezh2, like most other histone lysine methyltransferases (HKMTs), PRC2 contains a SET domain that is an evolutionarily conserved sequence motif identified in the *Drosophila* PEV (position effect variegation) suppressor SU(VAR)3-9, the *Polycomb*-group protein Enhancer of Zeste, and the *trithorax*-group protein Trithorax. Work Reinberg and others demonstrated that this class of protein establish a restrained state of transcriptional repression during development, whereas perturbations of this system can have profound consequences for cancer cells. Reinberg became interested in the potential role of Ezh2 in prostate cancer based on studies reported by others in which gene expression profiling revealed a correlation of Ezh2 expression and the development of prostate cancer. He is collaborating with Dr. Shen to develop mutant mouse models for Ezh2 to investigate its role in the development of prostate cancer. Dr.

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~~To further strengthen the Prostate Program's expertise in AR signaling, program leaders recruited Dr. Chih-Cheng Tsai. Dr. Tsai's early work identified and characterized a Drosophila transcriptional co-repressor, called SMRTER (Tsai et al., 1999). SMRTER is a Drosophila cognate of vertebrate SMRT (Silencing Mediator of Retinoic and Thyroid hormone Receptor) and N-CoR (Nuclear receptor Co-Repressor), which are known to bind the AR in an antagonist-dependent fashion. His recent research indicated that many of the known properties of AR, including its hormone-dependent nuclear localization, transcriptional activation, and chromosomal binding can be recapitulated in flies. Taking advantage of the observation that ectopic expression of AR in Drosophila eyes perturbs eye morphogenesis, Dr.Tsai will examine how this AR-mediated eye phen~~ ... [28]

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Reinberg, working in collaboration with Abate-Shen, recently found that Ezh2 overexpression is inversely correlated with methylation of lysine-27 in prostate tissues. These data have important implications for the mechanisms by which Ezh2 contributes to prostate cancer.

Activation of the transcription factor NF–κB leads to expression of several genes and an array of biological consequences including resistance to apoptosis and stimulation of cell proliferation. Arnold Rabson received GPCC Developmental Funds to apply his expertise in this areas to the study of prostate cancer. In collaboration with Celine Gelinas (Transcriptional Regulation and Oncogenesis Program), they found that NF-κB is constituitively activated in androgen-independent prostate cancer cells but not in androgen-dependent cell lines. Evidence of nuclear localization of NF-κB protein, indicative of activation, was also identified in tumor tissue samples of intermediate-grade prostate adenocarcinoma obtained through the CINJ Tissue Retrieval Service (Suh et al., *Prostate*, 2002). Studies in Rabson's laboratory are currently directed at defining the mechanisms responsible for constitutive activation of NF-κB and the consequences of this activation for the development and treatment of prostate cancer. He is collaborating with clinical scientists to develop therapeutic approaches to inactivate NF-κB in several forms of malignancy including prostate cancer.

Ramsey Foty developed novel explant assays to investigate how the biophysical properties of prostate cells correlate with their invasive potential. He used tissue surface tensiometry (TST), a novel *in vitro* method that measures elasticity, viscosity, and cohesivity (Dugay et al., *Dev Biol*, 2003; Robinson et al., *J. Cell Sci*, 2003; Ryan et al., *Proc Natl Acad Sci USA*, 2001; Foty and Steinberg, *Int J Dev Biol*, 2004a; Robinson et al, *Mol Biol Cell*, 2004; Winters et al., *Int J Cancer*, 2004). For comprehensive reviews see Foty and Steinberg, Int J. Dev Biol, 2004a and 2004b. They compared normal and malignant prostate to determine whether TST is an accurate predictor of the invasive potential of prostate tumors, how changes in the tumor microenvironment influence biophysical and invasive properties, and how changes in stromal components, including smooth muscle cells and fibroblasts, influence the elastic and viscous properties of tumors. Foty's lab demonstrated that invasive behavior of prostate carcinoma cell lines is correlated with tumor cohesivity as measured by TST (Foty et al., *Surgical Forum*, 1999). They also established a 3D *in vitro* co-culture system used to investigate the degree and rate of compaction of invasive cancer cells. They demonstrated that the degree of compaction is correlated with increased aggregate cohesivity as measured by TST. These assays are being adapted for rapid and quantitative approaches to address how potential therapeutic agents affect the biophysical properties of prostate cancer cells, and thereby affect invasive potential.

In the burgeoning field of gene therapy, a major limitation is the ability to control delivery of therapeutic genes specifically to cancer cells, since these vectors are often designed to produce cell death. Monica Roth's laboratory established a novel approach to the design of retroviral vectors for specific delivery into prostate cancer (Bupp and Roth, *Mol Ther*, 2002; Bupp and Roth, *Hum Gene Ther*, 2003). She is taking advantage of the fact that retroviral entry into cells is controlled by the surface envelope (Env) protein, which can be altered by replacement of a ten amino acid peptide sequence in the cell-targeting region. By screening libraries of retroviral Env proteins with random peptides substituted into this region, she identified novel Env isolates that efficiently deliver a gene to PC-3 human prostate tumor cells. These "designer" Env proteins will be important reagents in the development of gene therapy for prostate cancer and other malignancies.

Abate-Shen and Shen developed a series of mouse models that recapitulate the stages of prostate epithelial transformation (Bhatia-Gaur et al., *Genes Dev*, 1999; Abate-Shen and Shen, *Genes Dev*, 2000; Abate-Shen, *Nat Rev Cancer*, 2002; Abate-Shen and Shen, *Trends Genet*, 2002; Kim et al., *Cancer Res*, 2002; Kim et al., *Proc Natl Acad Sci U S A*, 2002; Abate-Shen et al., *Cancer Res*, 2003). Their efforts were accelerated through a grant from the Mouse Models of Human Cancer Consortium. These models are based on the loss-of-function of three genes implicated in human prostate cancer; the *Nkx3.1* homeobox gene, the *Pten* tumor suppressor gene, and the $p27^{kip1}$ cell-cycle regulatory gene. *Nkx3.1* single-mutant mice provide a

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Dr. Danny Reinberg has recently embarked on prostate cancer research through his analyses of factors that alter chromatin structure to regulate gene expression (Kuzmichev et al., 2002; Nishioka et al., 2002a; Nishioka et al., 2002b). They isolated one such factor from Hela cells, which they termed PRC2, and found that it methylated lysine-27 on the histone H3 tail. They further showed that the enzymatic activity of PRC2 resides in a polypeptide termed Enhancer of Zeste (Ezh2). Ezh2, like most other histone lysine methyltransferases (HKMTs), contains a SET domain, which is an evolutionarily conserved sequence motif identified in the *Drosophila* PEV (position effect variegation) suppressor SU(VAR)3-9, the *Polycomb*-group protein Enhancer of Zeste, and the *trithorax*-group protein Trithorax. Work by Reinberg an... [30]

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model for prostate cancer initiation and were used to develop a novel assay to investigate the precursor-product relationship of prostate intraepithelial neoplasia (PIN) to cancer (Bhatia-Gaur et al., *Genes Dev,* 1999; Kim et al., *Cancer Res,* 2002). These mutant mice provided important insights into the molecular mechanisms underlying the earliest stages of prostate cancer development and give investigators access to tissues that are difficult to consistently obtain from humans. These models display features of the human disease and provide insights into prostate cancer causation. For example, Abate-Shen and Shen recently found that loss-of-function of *Nkx3.1* leads to increased oxidative damage to prostatic epithelium as a function of aging. Therefore, *Nkx3.1* mutants provide a model to study the consequences and prevention of oxidative damage with naturally occurring antioxidants. During the next grant period this approach will be carried out in collaboration with Jeffrey Laskin and members of the Carcinogenesis and Chemoprevention Program.

By breeding compound mutant mice with loss-of-function of *Nkx3.1, Pten,* and/or $p27^{kip1}$, Abate-Shen and Shen produced models that ultimately progresses through localized adenocarcinoma to invasion and metastases (Kim et al., *Proc Natl Acad Sci U S A,* 2002; Abate-Shen et al., *Cancer Res,* 2003). Cancer progression in these mice increased with age, and the invasive tumors displayed morphological features highly reminiscent of human prostate cancer. Moreover, androgen-ablation led to androgen-independent prostate cancer and distant metastases. Thus, depending on the specific gene deletion and age of the mouse examined, these mutant mice provide pre-clinical models for studying chemoprevention, angio- and lymphangiogenesis, and for testing new chemotherapeutic agents. For example, ongoing studies being conducted in collaboration with DiPaola, examine the effectiveness of calcitriol for chemoprevention in mice and man. Other studies are planned to investigate the consequences of inhibiting Akt function in the acquisition of an androgen-independent phenotype (*vide infra*).

Shen is developing new mouse models for tracking tumor growth and metastases using high-resolution imaging. This strategy entails generation of a knock-in targeting allele to serves as a permanent imaging marker for tracking prostatic epithelial cells, thereby allowing investigators to follow tumor growth as well as emerging metastases. These mouse models facilitate studies designed to understand the biology behind tumor invasion, as well as the molecular events that allow transformation from androgen-dependent to independent-growth. Imaging approaches will enable more efficient drug testing, since they will permit investigators to asses the effects of treatment without sacrificing the animals.

Therefore members of the Prostate Program supported by the GPCC include some of the nation's leaders in understanding the molecular changes that underlie the development of normal and abnormal prostatic epithelium. They have identified fundamental aspects of signaling pathways and transcription factors whose dysfunction may underlie prostate carcinogenesis. Members generated a unique series of models, summarized in Table 1; these permit investigation of all stages of prostate cancer development and enable investigators to study the molecular biology of disease progression. These models are also being used for pre-clinical studies to design effective strategies for therapy (Aim 2) and prevention (Aim 3). The Prostate Program recruited basic researchers, including those who were not previously involved in disease-based research, to study prostate cancer. We anticipate that during the next grant period this work, aimed at analyzing prostate growth and development, mechanisms of transcriptional control, and other fundamental aspects of prostate biology, will continue to inform studies on prostate cancer pathophysiology.

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Table 1. Mouse Models of Prostate Cancer Developed by Program Members

STAGE	MODELS	POTENTIAL USES	THERAPEUTIC TRIALS PLANNED OR IN PROGRESS
Pre-disposition to cancer (hyperplasia, dysplasia, and low-grade PIN)	Nkx3.1 mutants IGF-BP mutants	Design of new chemoprevention approaches; identification of prognostic indicators for patients at risk for prostate cancer.	Effectiveness of green tea for preventing prostate cancer (planned); role of dietary factors in cancer initiation (planned): role of oxidative damage in carcinogenesis (ongoing).
Early stages of cancer progression (high-grade PIN; carcinoma in situ)	IGF-BP/p53 compound mutants; "young" Nkx3.1/Pten compound mutants	Design of new chemo-prevention approaches; identification of prognostic indicators for early-stage disease	Effectiveness of calcitriol in cancer prevention (ongoing); consequences of androgen-signaling for cancer progression (ongoing).
Overt carcinoma (locally invasive adenocarcinoma)	HMGA2 transgenic mice; aged Nkx3.1/Pten compound mutants	Design of new anti-cancer drugs; identification of pathways of progression	Consequences of using combinations of 2-deoxyglucose or mTOR inhibitors (planned).
Advanced disease (androgen-independence and metastases)	Androgen-ablated Nkx3.1/Pten compound mutants	Design of new chemotherapeutic approaches; identification of molecular correlates that distinguish androgen-dependent and independent stages of disease.	Androgen-ablation combined with mTOR inhibition and/or 2-deoxyglucose (planned).

2. To build on fundamental knowledge to develop effective therapeutic approaches for the treatment of prostate cancer.

RATIONALE/CANCER FOCUS: The Prostate Program strives to develop the biological basis for more effective methods of treatment and prevention. Program members design and conduct mechanistic-based clinical trials built on both laboratory findings and clinical observations. Members also provide national leadership to improve the treatment of prostate cancer. The mechanisms underlying the development of prostate cancer and the progression from *in situ* to invasive disease and then from hormone-sensitive to hormone-resistant disease are themes that are being analyzed. Investigators pursued the molecular mechanisms of drug resistance, developed strategies to circumvent resistance with early therapy, and used novel approaches to abrogate resistance mechanisms. Summarized below are examples of these research accomplishments.

ACCOMPLISHMENTS: As elegantly demonstrated by many studies in human prostate cancer, as well as the cell culture and mutant mouse models described in Aim 1, the development of neoplastic prostate epithelium results from progressive alterations of pathways that regulate normal cell growth and differentiation. Program members conduct studies in parallel to determine if this progression pathway can provide insights into mechanism of drug resistance. For example, William Hait worked with DiPaola to understand the basis for the refractory nature of prostate cancer to therapy. The CINJ Tissue Retrieval Service enabled the study of sequential expression of drug-resistance gene products in 95 human prostate cancer specimens obtained from patients who had not received hormonal treatment or chemotherapy (Sullivan et al., *Clin Cancer Res*, 1998). As benign glandular epithelium progressed through low-stage, low-grade prostate neoplasia to high-grade, high-stage disease, there was a serial increase in expression of several determinants of drug resistance. Notably, they found evidence for p53 mutations in 15-20% of

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early prostate cancers that markedly increased with advancing stage and grade of disease. In addition, this work suggested that p53 might regulate the expression of determinants of drug sensitivity such as topoisomerase II-α and the multidrug resistance protein gene, *MRP1*. They went on to show that *MRP1* is transcriptionally regulated by p53 (DiPaola and Aisner, *Semin Oncol*, 1999; Sullivan et al., *J Clin Invest*, 2000; Yang et al., *Mol Cancer Res*, 2003) and that MRP1 protein decreased accumulation and increased efflux of the antiandrogens, but had no effect on dihydrotestosterone accumulation; *a posteriori* evidence that in the face of p53 mutation and MRP overexpression, androgens might reach their receptors but anti-androgens might not. These results provided a mechanistic basis for the expectation that the use of chemotherapy late in the course of disease would be hampered by a panoply of drug resistance mechanisms and defined a previously unexpected mechanism of resistance to both chemotherapy and antiandrogen therapy in prostate cancer patients who had received neither form of treatment (DiPaola, *Semin Oncol*, 1999; Grzywacz et al., *Cancer Res*, 2003).

These data and other findings challenged the conventional wisdom that chemotherapy ought be used only after hormone ablation, and raised the hypothesis that early chemotherapeutic treatment of prostate cancer may lead to better outcomes. Therefore, DiPaola, Goodin and Todd conducted a series of chemotherapy-based clinical trials in patients before the initiation of hormonal therapy that included a series of laboratory correlates conducted in the DiPaola laboratory funded by several NCI R03 grants (DiPaola et al., *Clin Cancer Res*, 1997; DiPaola, *Semin Oncol*, 1999; DiPaola et al., *J Clin Oncol*, 1999; DiPaola et al., *Cancer*, 2001; Thalasila et al., *Cancer Chemother Pharmacol*, 2003). These investigator-initiated studies focused on patients with progression of disease based on increasing PSA who had not received hormonal therapy (Table 2). For example, mitoxantrone was studied in this early patients population and p53, bcl-2 and topoisomerase expression was assessed in available tumor samples (DiPaola et al., *Cancer*, 2001). Although the clinical activity of this agent was not strikingly different from historical data for treatment of more advanced disease, this trial laid the groundwork for studies of potentially more active and targeted agents in previously untreated patients.

Several additional lines of evidence suggested that p53 status may predict sensitivity to chemotherapy. In collaboration with Eileen White and Arnold Levine (Molecular Mechanisms of Tumor Growth), the Hait laboratory found that the functional status of p53 was closely associated with vinca alkaloid (e.g. vinblastine and vincristine) and taxane (e.g. paclitaxel) sensitivity. Whereas cells with wild-type p53 were relatively sensitive to vincas and resistant to taxanes, those with mutant p53 showed the opposite profile. They demonstrated that the expression of microtubule associated protein 4 (MAP4) was regulated by the transcriptional status of p53. Cells with mutant-p53 had increased expression of MAP4, increased polymerization of microtubules, and increased binding and sensitivity to taxanes (Zhang et al., *Oncogene*, 1998). In related studies, members of the Cancer Pharmacology/ Developmental Therapeutics and Breast Cancer Research Programs investigated the activity of epothilone B, a novel microtubule stabilizing agent whose transport is not affected by ATP Binding Cassette family transporters such as MRP1 or P-glycoprotein. DiPaola and White studied p53 status as a marker of sensitivity to epothilone B and demonstrated that this microtubule stabilizer was more cytotoxic to cells with mutant p53 (Ioffe et al., *Proc Amer Assoc Cancer Res*, 2003), consistent with the observations with taxanes. Based on these findings, DiPaola initiated a study of epothilone and estramustine in hormone-refractory prostate cancer (Table 2) and received Cancer Treatment Evaluation Program (CTEP) approval for developing this approach through ECOG. In this study the status of p53, MAP4 and MRP will be assayed to determine if they predict sensitivity to epothilones in the clinic.

DiPaola, Hait and White also demonstrated that overexpression of bcl-2 in model systems developed by the White laboratory blocked the collateral sensitivity to taxanes seen in p53 mutant cell lines. Since overexpression of bcl-2 had been observed in earlier studies of human prostate cancer specimens, DiPaola designed studies to abrogate this antiapoptotic mechanism. He identified cis-retinoic acid and alpha-interferon (CRA/IFN) as potent bcl-2 modulators that restored the sensitivity to taxanes in cell lines with

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mutant p53 and bcl-2 overexpression. He then carried out translational studies including an initial pilot study of the modulators alone in patients with prostate cancer (DiPaola et al., *Clin Cancer Res*, 1997; DiPaola and Aisner, *Semin Oncol*, 1999), followed by a series of phase 1 studies in combination with chemotherapy *(DiPaola et al., J Clin Oncol, 1999; DiPaola et al., Hematol Oncol Clin North Am, 2001; Thalasila et al., Cancer Chemother Pharmacol, 2003)*. These initial trials were funded by two R03 grants to DiPaola (CA77135; CA80654). The use of CRA/IFN was adopted by ECOG through a phase II study of CRA/IFN and paclitaxel in patients with hormone-refractory prostate cancer (E3899). An additional study based on these early findings is a DOD-funded, investigator-initiated trial of retinoic acid, alpha-interferon, taxotere, and estramustine ongoing at CINJ (DOD DAMD17-02-1-0229, PI:DiPaola). DiPaola's laboratory was the reference laboratory for measuring the effects of treatment on bcl-2 and other molecular correlates for the ECOG studies.

Recently, work by DiPaola and White has resulted in a DOD Idea Grant award (DOD W81XWH-05-1-0036). This was based on prior studies that demonstrated the dependence of early tumor growth and progression on anaerobic metabolism through glycolysis. In fact, the preference for tumor cells to depend on glycolysis over normal cells is the basis for the successful development of FDG-PET imaging. Despite these prior data, clinical development of agents that target glycolysis has been limited with initial concern over the lack of a therapeutic window. However, more recent studies have demonstrated that abnormal growth factor and apoptotic pathways, required by tumor cells to resist multiple insults, can drive tumor cells to even further dependence on glycolysis, supporting a rationale for selectivity of abrogating glycolysis in tumor cells compared to normal cells. For example, studies have recently demonstrated that activation of Akt kinase, which occurs commonly in tumor such as prostate cancer that are PTEN deficient, increases dependence of glycolysis. To test agents capable of abrogating the induction of glycolysis, we set up a laboratory co-culture model that could detect the growth effect of autocrine stimulation by tumor cells. Using two dimensional (2D) in-gel electrophoresis (DIGE) and Mass spectrometry, we found that initial changes consisted exclusively of induction of multiple glycolytic enzymes (Dvorzhinski et al., *Proteomics*, 2004). To determine if specific molecular mechanisms are dependent on the induction of glycolysis, we created isogenic cell lines derived from rat prostate epithelial cells transformed with both the adenovirus E1A protein to disrupt RB and a dominant negative form of p53, p53 DD (inactivation of RB and p53 pathways are sufficient for transformation and immortalization of primary rodent epithelial cells) in the laboratory of Dr. E. White. Into this genetic background we have introduced a Bcl-2 expression vector along with a constitutively active form of Akt, myr-Akt, H-Ras, and K-Ras. We have already began to test 2-deoxyglucose, an inhibitor of glycolysis, and found we could decrease the expression of glycoltyic enzymes in the co-culture model, inhibit cell growth at concentrations below what can be obtained safely in humans, and have cytotoxicity independent of Bcl-2 overexpression and Akt activation. The co-culture model and isogenic cell lines form a basis to continue further laboratory and clinical studies to determine the optimal approach to abrogation of glycolysis and mechanisms of sensitivity to such modulation.

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Table 2. Investigator-Initiated Therapeutic Trials in Prostate Cancer

TRIAL	STATUS	LABORATORY BASIS AND CORRELATE	N	COLLABORATORS
Early-Stage/Hormone-Naive Prostate Cancer				
Phase I study of taxotere and radiation in high-risk localized disease	Completed; *ASCO Proceedings*, #772, 2002; *J. Clin Oncol*, 2004)	n/a	30	Kumar DiPaola Weiss
Assessment of molecular markers of drug resistance	Completed; (Sullivan et al., *Clin Cancer Res.* 1998)	p53, bcl-2, MRP,	98	Hait, Amenta
Phase II study of 13 cis retinoic acid and alpha-interferon (CRA/IFN)	Completed; *(DiPaola et al., Clin Cancer Res. 1997)*	Serum TGF-beta and IGF-1	30	DiPaola Weiss Cummings
Serum PK activity with androgen naïve patients	Completed; (Cvijic et al., *Clin Cancer Res.* 2000)	PK activity in serum	14	Chen DiPaola
Phase II study of mitoxantrone	Completed; (DiPaola et al., *Cancer*, 2001)	Bcl-2, p53, and topo II	23	DiPaola, Weiss Todd
Phase II study of onconase and tamoxifen	Completed; *(Eid et al. Urol Res,* 2001)	Serum IGF-1 and TGFbeta	13	DiPaola, Weiss, Todd
Phase II study of Gleevec	Completed; *(Rao et al. Proc ASCO*, 2003; *The Prostate*, 2004)	PDGF immunohistochemistry	21	DiPaola, Goodin
Phase II study of pox PSA vaccine	Completed; *(Kauffman et al. Proc ASCO*, 2002; *JCO*, 2004)	T-cell immunity (ELISPOT)	70	Kaufman, DiPaola
Phase II study of docetaxel	Completed; *(Goodin et al., Proc ASCO*, 2003, *JCO* in Press)	Peripheral blood mononuclear cell bcl-2	25	DiPaola Weiss Goodin
Advanced/Hormone-Refractory Prostate Cancer				
Phase I study of CRA/IFN combined with chemotherapy	Completed; (DiPaola et al., *J Clin Oncol*, 1999)	Bcl-2 in peripheral blood mononuclear cells, PK, P450 evaluation	25	E. White, DiPaola
Phase I study of CRA/IFN combined with weekly paclitaxel	Completed; (Thalasila et al., *Cancer Chemother Pharmacol*, 2003)	Bcl-2 in peripheral blood mononuclear cells	15	E. White, DiPaola Rubin
Phase I study of bcl-2 antisense in HRPC (PI at MSKCC with collaboration for lab correlate)	Completed; (Morris et al., *Clin Cancer Res*, 2002)	Collaboration with main PI at another institution for bcl-2 laboratory studies	20	MSKCC DiPaola (lab component)
Phase I/II study of novel PSA activated peptide-doxorubicin	Completed; (DiPaola et al., *J*	PK of peptide and conjugate	30	DiPaola

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Phase I study of pox PSA/TRICOM vaccine	Completed; *DiPaola et al., Proc AACR, 2004*	T-cell immunity (ELISPOT)	10	DiPaola Lattime
Phase II study of docetaxel and vinorelbine	*Completed: Goodin et al., Proc ASCO*, 2002, *Ca Chem Pharm* 2005 In Press)		40	DiPaola
E3899: A randomized phase II study of CRA/IFN and paclitaxel vs. estramustine, mitoxantrone, and vinorelbine	Completed; *DiPaola et al., Proc ASCO, 2004*	Bcl-2 in peripheral blood mononuclear cells	70 (National)	DiPaola E. White
Phase I and II study of CRA/IFN combined with estramustine and docetaxel (RITE)	Ongoing: *Elsyad et al., Proc ASCO, 2004*	Bcl-2 in peripheral blood mononuclear cells, PK,	10	DiPaola Rubin E. White
Phase I/II study of estramustine in combination with epothilone	Completed; *Wojtowicz et al., Proc ASCO, 2004*	PK	15	DiPaola Rubin
Phase II study of estradiol patch as salvage therapy	Ongoing	Plasma estrogenicity by yeast assay	11	Lambert DiPaola
Phase II study of licorice root derivative combined and docetaxel	Ongoing	Estrogen yeast assays of patient serum		Lambert Gallo DiPaola

Although the focus of the Prostate Program is on investigator-initiated, translational research, CINJ members are also active participants in ECOG and intergroup trials, as well as cooperative efforts with other cancer centers. This work is promulgated by the recent appointment of DiPaola as Chair of the ECOG Genitourinary Committee. In this administrative role, DiPaola is responsible for the development of studies within the committee, as well as serving as principal investigator on a number of studies. Approved and developing studies (in addition to those shown in Table 2) that DiPaola will serve as chair or co-chair include the use of epothilone as a salvage therapy in prostate cancer and a randomized phase III study of Prostvac™ vaccine in combination with GM-CSF in patients with PSA progression after local therapy. The latter is based data from a vaccine trial completed through ECOG demonstrating that the optimal vaccine schedule was a "prime and boost" approach (E7897, Kaufman et al., *JCO* 2004, *Proc. ASCO*, 2002, DiPaola *JCO*, 2004).

DISCUSSION: Program members identified critical determinants of drug sensitivity in human prostate cancer and elucidated novel mechanisms of resistance. These studies informed the development of investigator-initiated clinical trials designed to counter drug-resistance in patients with prostate cancer. The tremendous growth in this area emphasizes the success of this disease-based program in meeting one of the CINJ strategic goals--increasing translational research. However, CINJ also recognized the need for additional strength to complement the leadership of DiPaola. Accordingly, CINJ and the Department of Surgery recruited Ronald Morton, an nationally-recognized urologist who will head the Division of Urology at RWJMS. In addition, CINJ resources were made available to recruit a pathologist to focus on prostate cancer, as well as two medical oncologist to work with DiPaola and Todd. Dr. Mark Stein, medical oncologist was recruited to the GU team in July of 2004. This team of investigators will capitalize on the new mouse model of prostate progression from androgen-dependent to independent disease as preclinical models to investigate new approaches to prevent and/or treat this lethal transition.

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3. To improve the control of prostate cancer through early detection, prevention, and information dissemination.

RATIONALE/CANCER FOCUS: The control of prostate cancer will require more powerful methods of prevention, early detection, treatment, and dissemination of new information to populations at risk. A major thrust of the CINJ Division of Prevention, Control and Population Science (Carcinogenesis and Chemoprevention; Population Science Programs) is to develop effective chemopreventive strategies and apply these to populations at risk. Prostate Program members pursue basic research approaches to understand the molecular mechanism underlying disease initiation. These studies, as well as pre-clinical studies in mutant mice and cell lines will lead to mechanistic based approaches to prevention. The recent recruitment of a cancer epidemiologists who investigate screening and surveillance methods (Lu-Yao), as well as the nutritional basis of hormonally-derived cancers (Bandera) create a new interface with the Population Science Program. Therefore, the work conducted by members of the Prostate Program provides mechanistic basis for new and ongoing cancer control research.

ACCOMPLISHMENTS: The carcinogenic process often involves oxidative and inflammatory processes. For example, Drs. Abate-Shen and Shen recently found that loss-of-function of *Nkx3.1* led to increased oxidative damage to prostatic epithelium as a function of aging. Laskin utilizes rodent models to characterize the effects of oxidation on the bioactivation of carcinogens in the prostate (a tissue with limited cytochrome P540 activity) and how diet effects this process (Laskin et al., *J Toxicol Environ Health A*, 2000; Billack et al., *Biochem Pharmacol*, 2001; Laskin et al., *Adv Exp Med Biol*, 2001; Ahmad et al., *J Leukoc Biol*, 2002; Billack et al., *Am J Physiol Cell Physiol*, 2002). He recently received NCI R01 funding to investigate a previously unrecognized molecular target for preventive agents in the prostate discovered in collaboration with Diane Heck (Carcinogenesis and Chemoprevention). They demonstrated that catalase has dual effects in the prostate including the oxidation of carcinogens to DNA-reactive metabolites (Heck et al., *J Biol Chem*, 2003). They used cDNA clones to generate and characterized cell lines that overexpress catalase activity, an enzyme with high affinity for major genotoxic chemicals that induce prostate tumors when administered to rodents (3,2'-dimethyl-4-aminobiphenyl (DMAB); 2-amino-l-methyl-6-phenyl-imidazo(4,5- b)pyridine (PhIP); N-nitrosobis (2-oxopropyl) amine and; N-methyl-nitrosourea. PhIP is a heterocyclic amine produced during cooking that has only recently been identified as a prostate carcinogen. DMAB, a synthetic aromatic amine, is a member of a large family of aminobiphenyls synthesized by the chemical dye industry. The Laskin group went on to show that several important nutrients, in particular, ferulic acid, vanillic acid and epigallocatechin gallate, are effective and potent inhibitors of the newly discovered role of catalase in the prostate. During the next grant period, collaborative efforts are planned to validate this target in mouse models and in human prostate cancer, identify more potent and selective inhibitors, and initiate clinical trials to assess the development and progression of prostate cancer.

Paul Copeland recently received R01 funding to investigate selenium metabolism and is applying his work to prostate cancer. Djetary supplementation with selenium was reported to decrease total cancer mortality and specifically reduced the incidence of lung, colorectal and prostate cancers (Clark et al., *JAMA*, 1996; Copeland and Driscoll, *Biofactors*, 2001; Copeland and Driscoll, *Methods Enzymol*, 2002; Copeland, *Gene*, 2003). Copeland, a recently recruited authority of selenoproteins, hypothesized that increased dietary selenium is either acting through the production of selenoproteins or through the action of selenium-containing small molecules that have unknown function (Driscoll and Copeland, *Annu Rev Nutr*, 2003). Since many selenoproteins protect against oxidative damage, he is testing the hypothesis that the chemoprotective effect of selenium supplementation is through an increase in selenoprotein expression. He reasoned that if increased dietary selenium is primarily functioning through the selenoprotein pathway, then prostate cancer cells should have altered selenoprotein expression. Indeed, it has been observed that at least one selenoprotein is dramatically reduced in prostate cancer. Dr. Copeland is studying the effects of both increased selenium and increased selenoprotein synthetic capacity on prostate carcinogenesis in model systems. This work will be greatly enhanced through access to the mouse models available to program

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members. One of the ultimate goals is to identify means by which to modulate the efficiency of selenoprotein synthesis, ideally in a selenoprotein-specific manner.

It is estimated that millions of Americans use nutraceuticals for disease treatment and prevention. Among these numerous unregulated substances are a host of herbal preparations. DiPaola leads a team of investigators interested in the carcinogenic and anticarcinogenic effects of phytoestrogens, with the goal of identifying non-toxic agents for chemoprevention. This work began when DiPaola observed that many of his patients were self-medicating with PC-SPES, a Chinese herbal concoction that was widely used by men to self-medicate their prostate cancer. DiPaola, Hait, Gallo (Carcinogenesis and Chemoprevention) and Lambert described the biological actions and toxic side effects of PC-SPES. They demonstrated the presence of potent phytoestrogens that were a likely biological explanation for both the activity and side effects of this preparation, and emphasized the importance of further study of novel estrogens as active clinical agents in prostate cancer (DiPaola et al., *N Engl J Med,* 1998; Marks et al., *Urology,* 2002). They went on to show that the mixture was contaminated with synthetic substances; this eventually led to the banning of PC-SPES from the market (Marks et al., *Urology,* 2002).

Lambert and DiPaola initiated investigator-initiated clinical trials studying phytoestrogens and pharmaceutical estrogens (DiPaola et al., *N Engl J Med,* 1998; Rafi et al., *Anticancer Res,* 2000; Zhu et al., *J Nat Prod,* 2001; Zhu et al., *Phytochemistry,* 2001; Rafi et al., *J Agric Food Chem,* 2002). They began by testing the safety and efficacy of these substances in men with prostate cancer, with the goal of moving active, non-toxic compounds into prevention trials for men (e.g. African Americans) at high risk. This paradigm follows the successful methods used for tamoxifen in breast cancer. For example, they are studying the activity of licorice root for patients with early disease (NCI-funded project), licorice root combined with taxotere for patients with hormone-refractory prostate cancer (NCI-funded Pilot Project), and an estradiol patch in men with prostate cancer that is refractory to hormonal and chemotherapy (See Tables 2 and 3). In these studies plasma estrogenicity will be determined by a yeast reporter system sensitive to activation of both ER alpha and beta. Further laboratory studies by DiPaola and collaborators identified additional phytoestrogens from licorice root including a novel dihydrophenol (DHP) capable of inducing apoptosis, mitotic arrest, bcl-2 phosphorylation, and microtubule bundling, and filed and received patents for this discovery (Rafi et al., *J Agric Food Chem,* 2002). Recently, the interaction of DHP with AR was studied by computational modeling in collaboration with William Welsh (Cancer Pharmacology/Developmental Therapeutics) (Ai et al., *Chem Res Toxicol,* 2003). These results suggest that DHP could function both as an androgen-receptor antagonist and, unexpectedly, as an estrogen-receptor agonist. Drs DiPaola and Welsh are submitted a NCI grant in October 2004 to further characterize DHP as a lead compound with potentially "ideal" pharmacological characteristics for the prevention or treatment of prostate cancer.

Robert Weiss in collaboration with C.S. Yang (Carcinogenesis and Chemoprevention) (Yang et al., *Annu Rev Pharmacol Toxicol,* 2002; Ju et al., *Nutr Cancer,* 2003; Lambert et al., *J Nutr,* 2003), investigates the effects of green tea constituents in patients with prostate cancer, through clinical trials supported by GPCC Developmental Funds. As part of this trial, concentrations of green tea polyphenols in the prostate are measured following a single dose of green tea administered before prostate surgery.

Members are also beginning to use the mutant mice models described in section 1 (see Table 1) as pre-clinical tools to test chemopreventive agents and to follow these results with studies in the clinic. For example, Abate-Shen and DiPaola are studying the effects of calcitriol (1 alpha 25, dihydroxy-vitamin D3), a vitamin D derivative with antitumor effects *in vitro* and *in vivo*. Proposed mechanisms include the modulation of p21, p27, and the bax/bcl-2 interaction. In clinical studies, calcitriol was shown to slow the rise of PSA in patients with prostate cancer and appeared to enhance the anti-tumor effect of platinum compounds and taxanes. Drs. DiPaola and Abate-Shen initiated a pre-clinical study in *Nkx3.1* mutant mice to examine whether calcitriol can reduce the incidence of prostate cancer in these mice. Preliminary results

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Program members have been pursuing several investigator-based clinica ... [98]

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support the idea that calcitriol prevents the development of high-grade PIN. In parallel, DiPaola is conducting a randomized, trial of calcitriol in men with biopsy-proven high-grade PIN (Table 3). Tissue will be assessed before and after treatment to evaluate the effects of calcitriol in this high-risk population. High-grade PIN is associated with a 40-50 percent chance of developing prostate cancer. Autopsy series demonstrated that high-grade PIN occurs as early as the fourth decade, and increases in incidence with age. Therefore, non-toxic agents that reduce this intraepithelial neoplasia would be candidates for larger prevention studies.

Table 3. • Investigator-initiated Prevention Trials in Prostate Cancer

TRIAL	STATUS	LABORATORY BASIS AND CORRELATES	N	COLLABORATORS
Phase II study of calcitriol in patients with PIN	Ongoing	Preclinical mouse experiments; transcriptional and translational profiles.	NA	Abate-Shen DiPaola
Assessment of phytoestrogens in PC-SPES in patients with androgen naïve prostate cancer in man and animals	Complete; (DiPaola et al., *N Engl J Med,* 1998; Marks et al., *Urology,* 2002)	Estrogen yeast assays *in vitro* and *in* vivo mouse experiments	8	DiPaola Gallo Lambert
The effect of soy on testosterone and PSA	Complete; (Goodin et al., Proc ASCO 2004)	Serum LH, Test, PSA	15	Lambert Goodin DiPaola
Phase II study of licorice-root derivative in patients with HNPC.	Ongoing	Estrogen yeast assays of patient serum	16	Lambert Gallo DiPaola
Assessment of Green tea in patients with prostate cancer	Ongoing	Tumor chemistry/apoptotic markers	15	Weiss C.S. Yang

Members strive to develop better methods of early detection and to use screening approaches responsibly and effectively. For example, Weiss collaborates with Armand Sarveysian to investigate the utility of mechanical imaging of the prostate (Perrotti et al., *J Urol,* 1999; Perrotti et al., *Urology,* 1999). They developed a device that detected nodules in prostate phantoms with a sensitivity exceeding that of an experienced urologist. In contrast to digital rectal exam, the results with mechanical examination were independent of the operator's experience. Therefore, the system appears to be a promising means of increasing the accurate and reproducible detection of abnormalities within the prostate (*Urology,* 2001).

The widespread use of PSA testing remains an area of intense investigation. Morton (Muldoon et al., *J Rural Health,* 1996; Witte et al., *Urology,* 1999; Kim et al., *Cancer Res,* 2000; Link and Morton, *Urol Clin North Am,* 2001) received NCI funding to develop a simple, sensitive technique to monitor PSA. This research is based on the fact that PSA testing methods remain both inconvenient and costly when applied to screening. Dr. Morton designed a prototype biosensor chip for quantitating blood PSA levels. This chip is an amperometric immunosensor, which would form the core of an inexpensive handheld device for measuring PSA at the bedside or in the physician's office. A critical goal of this project will be to produce a fusion molecule that shares PSA immunoreactivity and glucose oxidase enzymatic activity. This conjugate molecule will compete with PSA at the chip surface and thereby couple immune recognition to an easily detectable electrical signal. A device of this type should significantly impact the diagnosis and treatment of prostate cancer by lowering the cost and broadening the availability of PSA testing for all patients at risk.

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This is of particular concern given the striking racial differences in prostate cancer mortality, which may be attributable to inadequate access to PSA screening in medically underserved populations.

Dr. Morton will also collaborate with Grace Lu-Yao, a recently recruited prostate cancer epidemiologist, to study the impact of PSA testing on the practice of urology (Lu-Yao et al., *J Urol,* 1997; Lu-Yao and Yao, *Lancet,* 1997; Lu-Yao et al., *Urology,* 1999; Lu-Yao et al., *Bmj,* 2002; Lu-Yao et al., *J Natl Cancer Inst,* 2003). For example, using cancer registry data and intention-to-treat methodologies, Dr. Lu-Yao showed that prostate-specific 10-year survival for low-grade cancers was similar after prostatectomy, radiotherapy and conservative management, but survival of patients with high-grade cancers was significantly better after prostatectomy. She also examined the rates of radical prostatectomy in Medicare beneficiaries before and after the introduction of PSA testing. The results showed a rapid increase in radical prostatectomies following the introduction of PSA testing followed by a sharp decline seen particularly in older and white men. A third study examined the interval after PSA screening and subsequent risk of incurable prostate cancer. Using men 65 years old or older from nine SEER registries, she found that among those diagnosed with prostate cancer, the risk of non-localized cancer did not differ between those tested two or three years prior to diagnosis and those tested one year prior to diagnosis. However, the rate of prostate biopsy was directly related to the number of PSA tests performed (Yao and Lu-Yao, *J Urol,* 2001). Dr. Lu-Yao used SEER and Medicare data to compare rates of screening, treatment and mortality. These data showed that higher rates of PSA screening, prostate biopsy, radical prostatectomy, and external beam radiotherapy did not affect the adjusted mortality odds ratios in elderly patient populations (Lu-Yao et al., *Bmj,* 2002). In a recent report, Dr. Lu-Yao investigated the use of PSA screening in elderly men (Lu-Yao et al., *J Natl Cancer Inst,* 2003). By using a nationally representative sample of 7889 men who participated in the 2000 National Health Interview Survey, she found that the rate of PSA screening among men aged 75 or older was 32.5%, which was greater than that of fecal occult blood screening among men despite lack of evidence suggesting a benefit in this elderly population.

Lu-Yao also investigates the utility of radical prostatectomies in elderly patients. She used Medicare claims from 1991 to 1994 to identify and quantify the types and risks of complications, re-hospitalization within 90 days, and mortality at 30 and 90 days after perineal or retropubic prostatectomy. On the basis of data from 101,604 men, they found that complications and readmission after prostatectomy are substantially more common than previously recognized, and that older age is associated with elevated surgical mortality and complications (Lu-Yao et al., *Urology,* 1999).

The work of Lu-Yao and Morton will be of critical importance to that of Mrs. Betty Gallo, a leading prostate cancer advocate. An important goal of the Prostate Program is to develop effective strategies for outreach into the community. This has been initiated through involvement of prostate cancer advocates under the tireless leadership of Gallo, who established strong ties with the minority community through the 100 Black Men organization and the Men's Health Network. These efforts include education and screening programs for the African American community, and will provide access to this population for the epidemiological and intervention studies. Ms. Gallo sits on the CINJ protocol review and monitoring committee to ensure the interests of the survivor and advocacy communities are represented.

A major goal of the Gallo Prostate Cancer Center (GPCC) Cancer Control and Education Program is the reduction of prostate cancer incidence, morbidity and mortality among the residents of the State of New Jersey. GPCC focused on cancer control including the education of the public in the State of New Jersey about early detection of prostate cancer, particularly the African community where the need and the risk are both the greatest and the study of novel mechanisms to improve education through understanding aspects of culture diversity. The only available treatments for prostate cancer that are curative require the identification of the disease at these early stages of its development. In order to achieve these goals a pilot project award was given to the 100 Black Men of New Jersey and the Men's Health Network (MHN), Washington, D.C. New Jersey ranks number 1 in per capita incidences of prostate cancer in the United

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States according to the American Cancer Society, Cancer Facts and Figures, 2003. In 1999 the Gallo Prostate Cancer Center in collaboration with the 100 Black Men of New Jersey, initiated a program to offer free prostate cancer education and screenings to African-Americans in New Jersey. Congressman Donald Payne and Congressman Robert Menendez collaborated with the center to initiate the education and screening program. The program was started in Essex County of New Jersey who has the highest incidence rate of prostate cancer in African-Americans in the state. The increase of awareness of prostate cancer was achieved through several mechanisms: i. Providing opportunity for more public education and screenings, ii. Preparing and distributing brochures to a variety of community places such as barber shops and churches, iii. Increasing our current outreach efforts to include not only African-Americans but also the male population as a whole. In 1999 there were no educational materials available for the African-American or Latino community about prostate cancer. In our collaboration with the 100 Black Men of New Jersey and the Men's Health Network the center developed culturally sensitive materials for these communities with specific information about that communities incidence rate (brochures attached). These materials were distributed at health fairs, Village Gatherings in underserved population areas, mostly intercity (organized by the 100 Black Men of New Jersey) and prostate cancer education and screening programs as well as distributed to other outreach programs at local hospitals including the Partners and Affiliate Network of the Cancer Institute of New Jersey. The Men's Health Network's primary goal is education and awareness about men's health issues. The program with the MHN has advanced the awareness of prostate cancer on a national and international level.

DISCUSSION: Members identified new mechanism of carcinogen activation, providing new targets for screening and prevention. The also developed new imaging technologies and critically assessed the widespread use of PSA testing. Although the Prostate Program is new, it has already acquired significant expertise in prevention and control research. Promising areas of research include the use of mouse models for discovery of carcinogenic substances, for identifying important new targets for chemoprevention, understanding the function of selenium and selenoproteins, and innovative work on herbal substances. Access to healthy patient populations for preventive trials will be greatly enhanced by the recruitment of Morton, who will expand the Urology service, and the arrival of epidemiologists to take advantage of the strong ties with the African American community. Morton has considerable experience in the training and dissemination of information to minority communities, thereby providing an even stronger link to the outreach and advocacy work of Gallo.

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Deleted: , which reflects the foundation of the ongoing basic and translational studies described in Aims 1 and 2. We anticipate that this focus of the Prostate Program will strengthen considerably over the next grant period, given the recent recruitment of Drs. Morton and Yao. In addition, the arrival of Dr. Morton will enable Dr. Weiss to devote a greater percentage of his time to his chemoprevention and imaging studies.

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Future Development

The Prostate Program is built on a strong foundation of laboratory, clinical, and population research. The models developed by program members are all very new; they will be extensively utilized for generating new hypotheses for translational studies. Several examples include the use of calcitriol in mouse models, the work on phytoestrogens, and the targeting of local activation of carcinogens in prostate tissue. The addition of high-resolution small animal imaging studies in collaboration with Jeffrey and Deborah Laskin (Cytokines, Cytokine Signaling, and Cancer) will improve the pre-clinical studies using these mutant programmatic collaborations. The appointment of DiPaola to the ECOG leadership will accelerate translation of many of the concepts developed by Prostate Program members. The ability to leverage CINJ Development Funds created a robust pilot project activity that will bring additional investigators into the field of prostate cancer research. Finally, the arrival of Grace Lu-Yao, Mark Stein and Ronald Morton as well as the recruitment of additional members with expertise in medical and surgical oncology and pathology will help the program build strong relationships with the Prevention, Control, and Population Science and with the Clinical Science Division of CINJ.

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5.1. Value Added by the Center to the Program¶
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CINJ adds value to the Prostate Programits programs by providing centralized shared resources, strong program leadership, and effective mechanisms to promote interprogrammatic collaborations and translational research. Some of these, as they pertain to the Prostate Program, are summarized as follows:¶
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Shared Resources: Every member of the Prostate Program uses CINJ shared resources. The most heavily used include the new Transgenic/knockout Core, DNA Sequencing, Analytical Cytometry/Image Analysis, Immunohistochemistry, Tissue Retrieval Service, Biometrics, Research Pharmacy, and the Office of Human Research Services. A brief summary of usage is provided below: ¶
¶
Transgenic/knockout core: Under the direction of Michael Shen, a member of the Prostate Program, this facility has been instrumental in developing most of the mouse models of prostate cancer described in this section. The core is heavily utilized by Drs. Cory Abate-Shen, Danny Reinberg, and Joseph Fondell, and is a vital component of the Program Project Application that has been submitted by these investigators. ¶
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Biometrics: The Biometrics Shared Resource provides several essential components of support for Program members. This shared resource participates in the planning of all clinical trials, prior tbeforeo review by the Scientific Review Board. In addition, the pre-clinical studies in mouse models also require the expertise of Dr. Weichung Joe Shi (Resource Manager) and colleagues for their appropriate design and implementation; Dr. Shih is a partipantparticipant in the program project application submitted by members of the prostate program. The Biometrics resource also provides essential advice and statistical support for the microarray studies that are being pursued by members of the program; these efforts have lead to the submission of an AACR abstract and manuscript in collaboration with Drs. Abate-Shen and Shen.¶
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DNA sequencingSequencing: This core is extensively used for DNA sequencing by program members who do mole ... [117]

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Table 4. • Use of Developmental Funds for Pilot Projects ... [118]

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Although a relatively new program, the Prostate Program is well-founded on a strong foundation of basic research into prostate cancer mechanisms, clinical studies in disease prevention and therapy, and effective strategies for cancer control. In addition, Program Members will continue to pursue the productive areas of research that have already emerged. In particular, the mouse models that have been described in Table 2 have been under development in recent studies; they will be more effectively utilized in the subsequent grant period as they continue to be developed and characterized. High-resolution small animal imaging studies will bolster the ability to pursue pre-clinical studies using these mutant mice. Clinical trials in the program are based on laboratory data, through intra and inter programmatic collaborations, as clearly shown by the breath and quality of investigator initiated trials in Table 2. This newly formed program has rapidly developed these relationships that will continue to expand in future years. Finally, an important aspect of future growth will be to bolster efforts in Urological Oncology, which will be achieved by the leadership of Dr. Ron Morton. In addition, Dr. Morton, DiPaola and Abate-Shen will be assisting in the recruitment of a pathologist, who will also serve to bridge the diverse research interest and will reinforce the already strong research collaborations¶
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EDUCATIONAL PROGRAMS FOR RESEARCHERS

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As part of the DOD grant award the center established an education program for the basic and clinical researchers.' This program included presentations by prostate cancer researchers from UMDNJ and Rutgers University interested in prostate cancer research and invited speakers who are experts in prostate cancer in order to initiate collaborations among prostate cancer researchers.

Prostate Program Retreat
December 11, 2003

9:00 Michael Shen, Ph.D. - Welcome and Introduction

9:15 Simon Cherry, Ph.D. - Keynote Speaker
SC Davis
Technologies for In Vivo Imaging of Mouse Models

10:15 Coffee Break

10:30 Michael Shen, Ph.D. - Introduction and Overview

10:50 Danny Reinberg, Ph.D. - Exh2 and Associated Proteins in Prostate Cancer

11:30 Michael Shen, Ph.D. - Analysis of Metastatic Disease in Mouse Models of Prostate Cancer

12:10 Lunch

12:30 Cory Abate-Shen, Ph.D. - Modeling Hormone Refractory Prostate Cancer in the Mouse

1:10 Joseph Fondell, Ph.D. - Analysis of AR-interacting Proteins and their Roles in Hormone-dependent and
Independent Transcriptional Regulation

2:00 Simon Cherry, Ph.D. - Pathology and Imagine Core

2:20 Michael Shen, Ph.D. - Mouse Knock-out Core

2:40 Cory Abate-Shen, Ph.D. - Prostate Technologies Core

3:00 Michael Shen, Ph.D. - General discussion and wrap - up

PILOT PROJECT AWARDS

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PILOT PROJECT GRANT PROGRAM

In the Spring of 2004 GPCC sponsored a pilot project grant program which is aimed at encouraging new research in prostate cancer. We received a total of 9 grant applications with 2 withdrawing. A panel of noted scientists was assembled to review the grants. We awarded three new pilot project grants for a one year period with possibility of funding for a second year.

The role of dietary selenium in prostate chemoprevention - Paul Copeland, Ph.D., PI

Androgen Receptor Corepressors in Prostate Cancer Progression - Joseph Fondell, Ph.D., PI

Insights into Prostate Cancer: Recruitment of Histone Lysine Methyltransferase Complexes to Chromatic through AR Interaction - Danny Reinberg, Ph.D., PI

The following pilot projects are in the second year of their support:

Effect of 12-0-tetradecanoylphorbol-13-acetate (TPA) on the Growth of Prostate Tumors - Alan Conney, Ph.D., PI

Genetic Studies of IGEBP Function during Prostate Tumorigenesis - John Pintar, Ph.D., PI

The UMDNJ Centers of Excellence funded one of the submitted projects for the first year starting July 1, 2002. We will be supporting the second year of the project through December of 2004 submitted by Dr. Carlos Molina. The project to be funded is:

Regulation of the Putative Tumor Suppressor ICEr in Prostate Cancer by PTEN and P13K Signaling - Carlos Molino, Ph.D., PI

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Co-Leaders: Cory Abate-Shen, Ph.D.,
Robert S. DiPaola, M.D.

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PUBLICATIONS AND GRANTS

Dr. Cory Abate-Shen Publications:

Abate-Shen, C., Banach-Petrosky, W.A., Sun, X., Economides, K.D., Desai, N., Gregg, J.P., Borowsky, A.D., Cardiff, R.D., and Shen, M.M. (2003). Nkx3.1; Pten mutant mice develop invasive prostate adenocarinoma and lymph node metastates. *Cancer Research* 63:3886-3890.

Bendall, A.J., Hu, G., Levi, G., and Abate-Shen, C. (2003). Dlx5 regulates chondrocyte differentiation at multiple stages. *Int. J. Dev. Biol.* 47:335-344.

Abate-Shen, C. (2003). Homeobox genes and cancer: New OCTaves for an old tune. *Cancer Cell* 4:329-330.

Shen, M.M., and Abate-Shen, C. (2003). Roles of the Nkx3.1 homeobox gene in prostate organogenesis and carcinogenesis. *Dev. Dyn.* 228:767-778.

Rouzankina, I., Abate-Shen, C., and Niswander, L. (2004). Dlx genes integrate positive and negative signals during feather bud development. *Dev. Biol.* 265:219-233.

Berman, D.M., Desai, N., Wang, X., Karhadkar, S.S., Renon, M., Abate-Shen, C., Beachy, P.A., and Shen, M.M. (2004) Prostate defects of Sonic hedgehod mutant mice are a consequence of androgen insufficientcy. *Dev. Biol.*, 267:387-398.

Lee, H., Habas, R., and Abate-Shen, C. (2004) Msx1 cooperates withhistone H1b for inhibition of transcription repression and myogenesis. *Science*, 304: 1675-1678.

Dr. Robert S. DiPaola Publications:

R.S. DiPaola, E. Rubin, D. Toppmeyer, J. Eid, D. Butzbach, D. Dvorzhinski, T. Capanna, M. Cairdella, W.J. Shih, S. Goodin and M.B. Todd. Gemcitabine Combined With Sequential Paclitaxel And Carboplatin In Patients With Urothelial Cancers And Other Advanced Malignancies. Med Sci Mont 9:15, 2003

Thalasila, A., Poplin, E., Shih, J., Dvorzhinski, D., Capanna, T., Doyle-Lindrud, S., Beers, S., Goodin, S., Rubin, E., and DiPaola, R. S. A phase I trial of weekly paclitaxel, 13- cis-retinoic acid, and interferon alpha in patients with prostate cancer and other advanced malignancies. Cancer Chemother Pharmacol, *52:* 119-124, 2003.

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Kumar, P., Perrotti, M., Weiss, R., Cummings, K., Todd, M., Goodsin, S., and DiPaola, R. The safety of concurrent docetaxel and 3-D conformal radiation therapy (CRT) in patients with high risk locaized adenocarinoma of the prostate. J Clin Oncol. 2004 May 15;22(10):1909-15.

Kaufman H, Wang W, Manola J, DiPaola RS, Ko YJ, Williams SD, Whiteside T, Schlom J, Wilding G, Weiner LM Prime/boost vaccination using poxviruses expressing PSA in D0 prostate cancer: preliminary results of ECOG 7897, a randomized phase II clinical trial. J Clin Oncol. 2004 Jun 1;22(11):2122-32.

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1: Eff Clin Pract. 2002 May-Jun;5(3):137-42. Related Articles, Links ¶

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Prostate biopsies in men with limited life expectancy.¶

Wasson JH, Bubolz TA, Yao GL, Barry MJ.¶

Center for the Aging, Dartmouth Medical School, Hanover, NH 03755-3862, USA. john.h.wasson@dartmouth.edu¶

CONTEXT: Authorities discourage prostate screening in men who are likely to die from causes other than prostate cancer. PRACTICE PATTERN EXAMINED: Use of prostate b ... [128]

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Oh WK, Kantoff PW, Weinberg V, JonesG, Rini BI, Derynck MK, Bok R, Smith MR, Bubley GJ, Rosen RT, DiPaola RS, Small EJ. Prospective, Multicenter, Randomized phase II trial of the herbal supplement, PC-SPES, and Diethylstilbestrol in Patients with androgen-independent prostate cancer. J Clin Oncol. 2004 Sep 15;22(18):3705-12.

Ioffe, M., Nelson, D., Rao, K., Goodin, S., White, E., and DiPaola, R.S. Epothilone induced cytotoxicity is dependent on p53 in prostate cells. Prostate. 2004 Nov 1;61(3):243

Rao K, Goodin S, Levitt MJ, Dave N, Shih WJ, Lin Y, Capanna T, Doyle-Lindrud S, Juvidian P, DiPaola RS. A phase II trial of imatinib mesylate in patients with prostate specific antigen progression after local therapy for prostate cancer. The Prostate, 61:2004.

Dmitri, Dvorzhinski, Anu. Thalasila, Paul. Thomas, Diedra. Nelson, Hong Li, Eileen. White, Robert S. DiPaola. A novel proteomic co-culture model of prostate cancer cell growth. Proteomics. 4:3268-3275, 2004.

Goodin, S., Medina, P., Shih, W.H., Capanna, T., Abraham, S., Rao, K.V., Doyle-Lindrud, S., Todd, M., and DiPaola, R.S. Docetaxel in patients with PSA progression after local therapy for prostate cancer. In Press J. Clin Oncol 2004

S. Goodin, Capanna, M. Cairdella, W.J. Shih, S. Goodin , M.B. Todd, and R.S. DiPaola. A phase II trial of taxotere and navelbine in patients with HRPC with and without prior chemotherapy. In Press Cancer Chemotherapy and Pharmacology, 2004.

P. Arlen, H. Kaufman, and DiPaola R.S., Pox Viral Vaccine Approaches. Submitted

Doyle-Lindrud S. and DiPaola RS. Future Directions of Therapy in Prostate Cancer Submitted

R. DiPaola and I. Thompson. Cooperative Group Clinical Trials in Prostate Cancer. Submitted. Urology.

RECENT GRANTS

Grant Agency:	Department of Defense
PI:	Hait, William N.
Project Title:	Regulation of drug sensitivity by functional status of p53 In human prostate cancer
Project Period:	7/01/01 - 7/31/04

Grant Agency:	NIH/NICHD
PI:	Abate-Shen, Cory
Project Title:	Characterization of Msx1 in murine embroygenesis
Project Period:	4/1/03 - 3/31/08

Grant Agency:	NIH/NCI
PI:	Abate-Shen, Cory
Project Title:	Role of Nkx3.1 in prostate development and cancer
Project Period:	7/1/03 - 6/30/08

Grant Agency:	Department of Defense
PI:	DiPaola, Robert S.
Project Title:	A phase I/II trial of 13-cis retinoic acid, alpha interferon, taxotere, and estramustine (R.I.T.E.) in hormone refractory prostate cancer (HRPC)
Project Period:	2/15/02 - 2/14/05

Grant Agency:	NIH/NCI/CCSG CAM Supplement
PI:	DiPaola, Robert S.
Project Title:	The effect of Glycrrhiza Glabra in patients with prostate Cancer
Project Period:	3/1/01 - 2/28/05

Grant Agency:	NIH/NCI/CCSG CAM Supplement
PI:	DiPaola, Robert S.
Project Title:	Assessment of licorice root in patients receiving Docetaxel Chemotherapy for prostate cancer
Project Period:	3/1/02 - 2/28/05

Grant Agency:	NIH/NCI/CCSG CAM Supplement
PI:	DiPaola, Robert S.
Project Title:	Assessment of estrogens from herbal therapies used on Prostate cancer
Project Period:	3/1/03 - 2/28/05

Grant Agency:	National Institutes of Health

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NOVEL THERAPIES IN CANCER OF THE PROSTATE:TARGETING BCL-2, Cancer Center Grand Rounds, University of Pennsylvania, Philadelphia PA, 1/99.¶
¶
NOVEL THERAPY FOR PROSTATE CANCER, Seminar, University of Oklahoma, 2/99.¶
¶
MODULATION OF PACLITAXEL CHEMOTHERAPY, Combined Medical and Radiation Oncology Grand Rounds, New York University, 3/17/99.¶
¶
A UNIQUE PERSPECTIVE IN THE TREATMENT OF PATIENTS WITH HORMONE SENSITIVE PROSTATE CANCER, Univ of Chicago, taxotere seminar,4/27/99¶
¶
PROSTATE CANCER, Grand Rounds, St.Vincent's Hospital, Staten Island, 5/6/99¶
¶
NOVEL THERAPIES FOR PROSTATE CANCER, Oncology Grand Rounds, St. Elizabeth Hospital. NJ, 5/13/99 ¶
¶
WEEKLY TAXOL/RETINOID/INTERFERON IN PROSTATE CANCER, MD Anderson W.I.S.E. conference, NY Palace Hotel, NY, 12/18/1999 ¶
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2000¶
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TAXOL/RETINOID/INTERFERON FOR HORMONE REFRACTORY PROSTATE CANCER, Fox Chase Investigators Meeting, Mandalay Bay, Lanai, 3/16/2000 ¶
¶
THE ROLE OF CHEMOTHERAPY FOR PROSTATE CANCER, BMS Symposia, Las Vegas, 3/2000¶
¶
ASCO UPDATE ON PROSTATE CANCER, BMS Symposia, Las Vegas Nevada, 6/30/2000 ¶
¶
NOVEL THERAPY IN PROSTATE CANCER, Medical Oncology Symposia, Seattle WA. 8/10/2000 ¶
¶
RETINOID, INTERFERON AND TAXOL RANDOMIZED AGAINST ESTRAMUSTINE, NAVELBINE, AND MITOXANTRONE, Glaxo Advisory Board, Denver CO, 8/25/2000 ¶
¶
OVERVIEW OF PROSTATE CANCER, Distinguished lecture, Brookdale Medical Center, NY, 9/6/2000 ¶
¶
AVENTIS ADVISORY BOARD MEETING, Lake Tahoe Nevada, 9//19/2000¶ ... [134]

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PI:	Conney, Alan
Project Title:	TPS on leukemia and solid tumors
Project Period:	7/1/03 - 6/30/06

FUTURE FUNDED GRANTS:

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Grant Agency:	National Institutes of Health
PI:	DiPaola, Robert S.
Project Title:	The Effect of Glycolytic Modulation on Prostate Cancer
Project Period:	November 2004

Grant Agency:	Department of Defense
PI:	Hait, William N.
Project Title:	The Dean and Betty Gallo Prostate Cancer Center
Project Period:	January 2005

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DESCRIPTION. State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This description is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. DO NOT EXCEED THE SPACE PROVIDED.

The Prostate Cancer Program unites investigators with broad and complementary expertise in prostate cancer research. The overall goal and unifying theme is to elucidate basic mechanisms of prostate growth and oncogenesis, with the ultimate goal of promoting new and effective strategies for the eradication of prostate cancer that will also lead to more effective strategies for prevention. . Members' have a wide range of research interests that collectively optimize the chances of providing new insights into normal prostate biology as well asand unraveling the molecular pathophysiology of prostate cancer. Studies in cell culture systems and powerful animal models developed by program members recapitulate the various stages of prostate cancer progression, including prostatic intraepithelial neoplasia, adenocarcinoma, androgen-independence, invasion and metastases. These models promise to further strengthenfurther strengthen an already robust program of investigator-initiated therapeutic clinical trials, including studies that have been developed adopted by national cooperative groups. on the national level. Efforts have now begun to translate laboratory studies of oncogenesisresults into clinical studies of early detection and chemoprevention are underway.

The specific goals of this program are:

1. To investigate the molecular mechanisms underlying normal prostate growth and differentiation and elucidate the molecular mechanisms underlying prostate oncogenesis.

2. To build on fundamental knowledge to develop effective therapeutic approaches for the treatment of prostate cancer.

3. To improve the control of prostate cancer through early detection, chemoprevention, and information dissemination. outreach and education

This new disease-based program is structured to improve interdisciplinary interactions and translational results. Already, through the dynamic leadership of Drs. Cory Abate-Shen and Robert DiPaola, new investigators were attracted to the field, new collaborations engendered, and numerous investigator-intiated trials implemented.

PERFORMANCE SITE(S) (*organization, city, state*)

The Cancer Institute of New Jersey
195 Little Albany Street
New Brunswick, New Jersey 08901

KEY PERSONNEL. See instructions on Page 11. Use continuation pages *as needed* to provide the required information in the format shown below.

Name	Organization	Role on Project
Cory Abate-Shen, Ph.D.	RWJMS	Program Leader – Prostate Cancer Program
Robert DiPaola, M.D.	RWJMS	Program Co-Leader – Prostate Cancer Program

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PLACEHOLDER FOR PROGRAM LEADER BUDGET PAGE PHS 398 EE

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PROSTATE PROGRAM
Program 067

Budget Narrative Justification
Program Leaders: Cory Abate-Shen, Ph.D., 5% Effort
Program Co-Leader: and Robert DiPaola, M.D., (5% Eeffort)

1. Credentials

Dr. Cory Abate-Shen, Ph.D., is a resident member of the Center for Advanced Biotechnology and Medicine, Professor in the Departments of Medicine and Neuroscience and Cell Biology at UMDNJ-Robert Wood Johnson Medical School, and holds a joint appointment in the Department of Medicine where she serves as and Chief of the Division of Developmental Medicine and Research. Dr. Abate-Shen completed her Ph.D. at Cornell University Medical College, and then pursued post-doctoral training in molecular oncology with Dr. Tom Curran at the Roche Institute of Molecular Biology. Her productive post-doctoral career fellowship included seminal observations on the redox regulation of the onco-proteins, Fos and Jun, which that culminated in many several high-impact prestigious publications.

Since establishing her independent laboratory in 1991, Dr. Abate-ShenAbate-Shen has been studyingstudied the functions of vertebrate homeoproteins in development and cancer. She, in collaboration with Dr. Michael Shen, identified the mouse *Nkx3.1* homeobox gene and characterized its expression and functions in the prostate; these studies served as an entry point for her successful foray into the field of generation of mouse models of human disease. of prostate carcinogenesis. These Her studies on models of the development of prostate cancer are now supported by several grants from the NCI and Department of Defense. ; in particular, Dr. Abate-ShenAbate-Shen is principal investigator for on a U01 grant from the NCI's Mouse Models of Human Cancer Consortium (CA084294), that which has recently been given a high priority for renewal.

Dr. Abate-ShenAbate-Shen's authority growing stature in the field of prostate cancer research is evident from her list of impressive publications and reviews in this area. She has also beenis invited sought after to present her findings at numerous international meetings and to has organized definitive conferences and symposia on

prostate cancer models. She is an Associate Editor of *Cancer Research*, on the Editorial Board of *Molecular Cellular Biology*, and has been a permanent and Ad *ad Hoc hoc* member of NIH Cell and Developmental Biology Study Sections. Among her many awards and honors, Dr. Abate-ShenAbate-Shen has been a Sinsheimer Scholar, an National Science Foundation Young Investigator, and the recipient of the Women in Cell Biology Junior Award from the American Society for Cell Biology.

Dr. Robert S. DiPaola, M.D., is Associate Professor of Medical Oncology in the Department of Medicine at UMDNJ-Robert Wood Johnson Medical School. Dr. DiPaolaDiPaola received his B.S. and M.D. degree from the University of Utah, where he graduated Summa Cum Laude and was elected to Alpha Omega Alpha. He completed his residency training at Duke University Medical Center and his fellowship in Hematology/Oncology at the University of Pennsylvania, which included training in the laboratory of Dr. Alan Gewirtz where he studied nucleic acid-based therapeutics.. Among his many awards and achievements, Dr. DiPaola received the investigator award of excellence by the Eastern Cooperative Oncology Group in 2003.

Since his arrival at CINJ inIn 1994, Dr. DiPaolaDiPaola has organized a multidisciplinary prostate programgenito-urinary oncology program at CINJ by attracting and , integrating members of Urology, Medical Oncology, Pathology, and radiation Radiation oncologyOncology. He has developed and activated multiple clinical trials for patients with prostate cancer, which offer new options for therapy, through his ability to establish effective interactionsclose interactions with laboratory scientists. He published the first definitive trial on PC-SPES, a Chinese herbal remedy used by many patients with prostate cancer. In this lead article in the *New England Journal of Medicine*, he defined the potent estrogenic activity of the preparation and suggested that this may account for both its therapeutic and toxic effects. He was also one of the earliest investigators to target the degradation of bcl-2 as a means to restore drug sensitivity in patients receiving chemotherapy.

with basic science laboratories at UMDNJ. He is a recognized authority inHis accomplishments in the area of prostate cancer research as are evidenced underscored by his grants from the NIH, Department of Defense, and private foundations, as well as his publications in prominent journals including the *New England Journal of Medicine*, *Clinical Cancer Research*, and the *Journal of Clinical Oncology*.
Among his awards and achievements, DiPaola received the investigator award of excellence from the Eastern Cooperative Oncology Group (ECOG) in 2003.
In 1997, Dr. DiPaolahe was elected chairman of the ACS task force for prostate cancer in New Jersey and chairman of the prostate scientific advisory group for the New Jersey Commission on Cancer Research. IOn a national level, n 2002, Dr. DiPaolaDiPaola was elected co-chair of the Genito-Urinary Group Committee at of the Eastern Cooperative Oncology GroupECOG in 2002. He serves as Chairman of a national trial in the ECOG [BOB -- SPELL OUT what it is] using agents that modulate tumor resistance in patients with hormone refractory prostate cancer. Dr. DiPaola's laboratory serves to assess biological correlates of this trial in samples sent from multiple ECOG institutions nationally. He is on the Editorial Board of the NCI *physician's Physician's data Data queryQuery*. He has lectured nationally at manyHis invited lectureships institutions, including include presentations to the at the National Academy of Science, and and has provided Grand Rounds at Dana FarbarFarber Cancer Institute, the University of Pennsylvania, Jefferson Medical Center and Albert Einstein Medical Center. He moderated sessions on translational research in Prostate prostate Cancer cancer at the American Association for Cancer Research Annual Meetings in 2002 and 2003, and will be a featured speaker speak at the American Society of Clinical Oncology Educational Sessions in 2004 on translational research in prostate cancer.

2. Role

The role of the co-leaders of the Prostate Program is to recruit investigators who are interested in pursuing research in prostate cancer, as well as and to assist their development in this area by providing the appropriate guidance and support. BSeveral years ago before the Prostate Program was formed, few investigators in our the

Rutgers/UMDNJ research community were pursuing prostate cancer research, and those that were had little few forum venues for interactions. Drs. Abate-Shen and DiPaola have now recruited several new investigators to pursue prostate cancer researchinto the field including, particularly among basic researchers scientists who had not previously been pursing attracted to disease-focused research. Many Several of the investigators that are now pursuing prostate cancer research were previously focused that are now pursuing prostate cancer research previously concentrated exclusively on basic mechanism of transcription and were drawn frommembers of the Transcriptional Mechanism and Oncogenesis Program headed by Dr. Arnold Rabson, who himself is alsonow also pursuing immersed in prostate cancer research.

Drs. Abate-Shen and DiPaola have also promoted intra- and inter-programmatic collaborations through monthly program meetings, retreats, workshops, and symposia., which have been organized through the Prostate Program. These meetings have fostered a sense of community, which has led leading to many subsequent interactions, as described herein. Drs. Abate-Shen and DiPaola interact with other Program Leaders through the monthly meeting of the Scientific Council, where presentations by program members are evaluated for potential interactions and translation into clinical application. Through this forum they also evaluate shared resources and identify the membership's need Another important role of the program leaders is to identify new opportunities for members for using shared resources and to provide feedback to the CINJ leadership regarding the use of such resources or the needs of their members to have access to additional shared resources as new technologies emerge. The program leaders regularly consult with program members regarding on issues and technologies that would promotethe ways and means to promote their research efforts. , including access to new areas of expertise, new resources and other technologies within our own community and the broader community. More generally, Tthe program leaders serve as facilitators for potential intra- and interprogrammatic collaborations. Finally, Drs. Abate-Shen and DiPaola set an example of promoting cross-disciplinary and translational research through their own multi-disciplinary collaborative research efforts.

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BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME POSITION TITLE

Cory Abate-Shen Professor and Division Chief

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION *(if applicable)*	DEGREE	YEAR(s)	FIELD OF STUDY
Fordham University	B.A.	1983	Psychology
Cornell University Medical College	Ph.D.	1988	Enzymology/Neurobiology
Roche Institute of Molecular Biology	Post-doc	1988-1991	Gene Regulation

RESEARCH AND PROFESSIONAL EXPERIENCE:

Professional Experience:

1983 – 1988	Graduate Research Assistant, Laboratory of Molecular Neurobiology, Cornell University (**Mentor**: Tong H. Joh)
1988 – 1991	Postdoctoral Fellow, Molecular Oncology & Virology, Roche Inst. of Molecular Biology (**Mentor**: Tom Curran)
1991 – 1997	Assistant Professor, Department of Neuroscience, UMDNJ
1991 – present	Resident Member, Center for Advanced Biotechnology and Medicine
1995 – present	Member, The Cancer Institute of New Jersey
1997 – 2001	Associate Professor (with tenure), Department of Neuroscience, UMDNJ
1999 – present	Scientific Leader, Prostate Cancer Program, The Cancer Institute of New Jersey
2001 – present	Professor, Departments of Medicine and Neuroscience, UMDNJ
2002 – present	Chief, Division of Developmental Medicine and Research, Department of Medicine

Professional Activities (recent):

1997 – 2002	Member, NIH Study Section, Cell Development and Function 4 (CDF-4)
1998 – present	Editorial Board, *Molecular and Cellular Biology*

1999 – present	Member, Steering Committee, Mouse Models for Human Cancer Consortium
2000 – present	Associate Editor, *Cancer Research*
2001	Organizer, "Modeling human prostate cancer in the mouse", NCI/ The Jackson Laboratories

Honors and Awards:

1983	Summa Cum Laude, Fordham University
1987	Vincent du Vigneaud Award for Excellence in Graduate Research, Cornell University
1992 – 1995	Sinsheimer Scholar Award
1993	Women in Cell Biology Junior Award, American Society for Cell Biology
1993 – 1998	NSF Young Investigator Award

Selected peer-reviewed publications: (from a total of 95)

Bhatia-Guar, R. Donjacour, A.A., Sciavolino, P.J., Kim, M., Desai, N., Young, P., Norton, C., Gridley, T., Cardiff, R.D., Cunha, G.R., **Abate-Shen, C.** and Shen, M.M. (1999). Roles for *Nkx3.1* in prostate development and cancer. *Genes Dev.* 13:966-977.

Bendall, A.J., Ding, J., Hu, G., Shen, M.M. and **Abate-Shen, C.** (1999). *Msx1* antagonizes the myogenic activity of *Pax3* in migrating limb muscle precursors. *Development* 126:4965-4976.

Yan, Y., Stein, S., Ding, J., Shen, M.M. and **Abate-Shen, C.** (2000). A novel PF/PN motif inhibits nuclear localization and DNA binding activity of the ESX1 homeoprotein. *Mol. Cell. Biol.* 20:661-667.

Abate-Shen, C. and Shen, M. (2000). Molecular genetics of prostate cancer. *Genes Dev.* 14:2410-2434.

Bendall, A. J. and **Abate-Shen, C.** (2000). Roles for MSX and DLX homeoproteins in vertebrate development. *Gene* 247:17-31.

Hu, G., Price, S., Shen, M.M. and **Abate-Shen, C.** (2001). *Msx* homeobox genes inhibit differentiation by upregulation of Cyclin D1. *Development* 128:2373-2384.

Hovde, S., **Abate-Shen, C.** and Geiger, J.H. (2001). Crystal structure of the Msx-1 homeodomain/DNA complex. *Biochemistry* 40:12013-21.

Pizette, S., **Abate-Shen, C.** and Niswander, L. (2001). BMP mediates vertebrate limb growth and dorsal-ventral patterning by differential use of two homeodomain proteins. *Development* 128:4463-4474.

Kim, M., Desai, N., Cardiff, R., Banach-Petrosky, W., Parsons, R., Shen, M. and **Abate-Shen, C.** (2002). Cooperativity of *Nkx3.1* and *Pten* loss-of-function in a mouse model of prostate carcinogenesis. *Proc. Natl. Acad. Sci. USA* 99:2884-2889.

Kim, M., Bhatia-Gaur, R., Banach-Petrosky, W., Desai, N., Wang, Y., Hayward, S., Cunha, G., Cardiff, R., Shen, M. and **Abate-Shen, C.** (2002). *Nkx3.1* mutant mice recapitulate early stages of prostate carcinogenesis. *Cancer Research* 62:2999-3004.

Abate-Shen, C. and Shen, M.M. (2002). Mouse models of prostate carcinogenesis.*Trends Genet.* 18:S1-S5 *(online)*.

Yan, Y.-T., Liu, J.-J., Luo, Y., E, C., Haltiwanger, R. S., **Abate-Shen, C.** and Shen, M. M. (2002). Dual roles of Cripto as a ligand and co-receptor in the Nodal signaling pathway. *Mol. Cell. Biol.* 22:4439-4449.

Park, J.H., Walls, J.E., Galvez, J.J., Kim, M., **Abate-Shen, C.,** Shen, M.M. and Cardiff, R.D. (2002). Prostatic intraepithelial neoplasia in genetically engineered mice. *Am. J. Path.* 161:727-735.

Abate-Shen, C. (2002) De-regulated homeobox gene expression in cancer: cause or consequence? *Nature Reviews Cancer* 2:777-785.

Bendall, A. J., Hu, G., Levi, G., and **Abate-Shen, C.** (2003) *Dlx5* regulates chondrocyte differentiation at multiple stages. *Int. J. Dev. Biol.* 47:

Abate-Shen, C., Banach-Petrosky, W. A., Sun, X., Economides, K. D., Desai, N., Gregg, J. P., Borowsky, A. D., Cardiff, R. D., and Shen, M. M. (2003) *Nkx3.1; Pten* mutant mice develop invasive prostate adenocarcinoma and lymph node metastases. *Cancer Research* 63:3886-3890.

Abate-Shen, C. (2003) Homeobox genes and cancer: New octaves for an old tune. *Cancer Cell.* 4:329-330

Berman, D. M., Desai, N., Wang, X., Karhadkar, S. S., Reynon, M., **Abate-Shen, C.**, Beachy, P. A., and Shen, M. M. Prostate defects of Sonic hedgehog mutant mice are a consequence of androgen insufficiency. *Dev.Biol.*, in press.

Shen, M. M. and Abate-Shen, C. (2003) Roles of the *Nkx3.1* homeobox gene in prostate organogenesis and carcinogenesis. *Developmental Dynamics* In press.

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BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
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NAME	POSITION TITLE
Robert S. DiPaola	Associate Professor of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Utah	BS	1984	Science
University of Utah	M.D.	1988	Medicine
Duke University Medical Center		1989	Internship
Duke University Medical Center		1991	Residency
University of Penn		1994	Oncology/Heme

Positions:

7/94-7/2001: Assistant Professor, The Cancer Institute of New Jersey, UMDNJ, Robert Wood Johnson Medical School

7/2001-Current: Associate Professor (with Tenure), The Cancer Institute of New Jersey, UMDNJ, Robert Wood Johnson Medical School RWJMS

7/2001-Current: Executive Director of the Dean and Betty Gallo Prostate Cancer Center.

1/2002-Current: Chair of the New Jersey Oncology Group.

HONORS:

1984 Summa Cum Laude, Phi Beta Kappa National Honor Society
1987 Alpha Omega Alpha, Medicine Honors, University of Utah
1993-1994 American Cancer Society Clinical Oncology Fellowship Award
1998 Voted in "Best Doctors in America"
2003 ECOG Investigator Award

COMMITTEES:

5/2002-Current Co-chair of GU committee at the Eastern Cooperative Oncology Group
4/2003 Grant study section, Department of Defense (DOD), breast cancer RFA
6/2002, 6/2003 Grant study section, DOD, Prostate cancer committee
5/2002-Current Co-chair of GU committee at the Eastern Cooperative Oncology Group
1/03 Member American Board of Internal Medicine (ABIM) committee
7/2000-Current Editor of the National Cancer Institute Physicians data query (PDQ)

PATENTS:

Title: Anti-carcinogenic activity of hydroxylated chalcone compounds, Filed: 12/20/2001, Patent number: WO0195923
Title: Compositions of Polygonum Odoratum for Prevention and Treatment of Disease, 2/1/2000, Patent number: 00-0061
Title:Novel Estrogenic Cytotoxic Flavonoid and Methods of its use, Filed: 12/20/99. Patent Number: RWJ-99-41 (Provisional)

PUBLICATIONS (selected):

DiPaola, R.S., Orel, S., Fowble, B.: Ipsilateral breast tumor recurrence after conservative surgery and radiation. Oncology, 8:59-68, 1994.

Luger, S.M., Ratajaczak, W.I., Kuczynski, W.I., DiPaola,R.S., Ngo, W., Clevenger, C.V., and Gewirtz, A.M.: A Functional analysis of Protooncogene Vav's Role Adult human hematopoiesis. Blood, 87(4): 1326-1334, 1996.

August, D.A., DiPaola, R.S., Hait, W. A Model of Comprehensive Diagnosis and Care for patients with Breast Cancer. New Jersey Medicine, 27-34, 1996

DiPaola, R.S. Treatment of Advanced Breast Cancer: How much Chemotherapy is Enough. Seminars of Oncology 23 (3): xv-xvi, 1996.

DiPaola, R.S., Kuczynski, W.I.., Onodera, K., Ratajczak, M., Hijiya, N., Moore, J. and Gerwirtz, A.M.: Evidence for a functional kit Receptor in Melanoma, Breast and Lung carcinoma cells. Cancer Gene Therapy, 4:176-182, 1997.

Salhany K.E., Feldman M., Kahn M.J., Peritt D., Schrentzenmair, R., Darren M., Wilson B.A.,DiPaola R.S., Glick, A.D. Kantt J.A., Nowell P.C. and Kamoun M. Hepatosplenic gamma/delta T Cell Lymphoma: Ultrastructural, Immunophenotypic, and Functional Evidence for Cyotoxic T Lymphocyte Differentiation. Human Pathology 28:675-685, 1997.

DiPaola, R.S., Goodin S., Ratzell M., Florczyk M., Karp G., Ravikumar T.S.Chemotherapy for Metastatic Melanoma During Pregnancy. Gynecologic Oncology 66:526-530, 1997.

DiPaola, R.S., Weiss, R.E., Cummings, K.B., Kong, F.M., Jirtle, R., Anscher, M., Gallo, J., Goodin, S., Thompson, S., Rasheed, Z., Aisner, J., and M. Todd. Effect of 13-cis Retinoic acid and alpha interferon on transforming growth factor Beta1 in Patients with Rising Prostate Specific Antigen. Clin Cancer Research, 3:1999-2004, 1997

DiPaola, R.S., Rodriquez, R., Goodin S., Recio A., Orlick M., Mollman J., Bird S., Belsh J., Schein P., Aisner J., Schuchter L. Amifostine and Dose Intense Paclitaxel in Patients Pts with advanced Malignancies. Cancer Therapeutics 1:11-17, 1998.

Silber JH, Fidman M, DiPaola RS, Erder MH, Pauly MV, Fox KR. First cycle blood counts and subsequent neutropenia, dose reduction or delay in early stage breast cancer therapy. J Clin Oncol 16:2392-2400, 1998.

DiPaola RS, Zhang H, Lambert G, Meeker R, Licitra E, Rafi MM, Zhu BT, Spaulding H, Goodin S, Toledano M, Hait W, Gallo M. Clinical and Biological activity of an estrogenic herbal combination (PC-SPES) in prostate cancer. N Engl J Med 339:785-791, 1998.

Goodin S. and DiPaola R.S. Strategies for Using Cytoprotective Agents to improve outcomes associated with Cancer Chemotherapy. Disease Managment and Clinical Outcomes 1(5): 292-301, 1998.

DiPaola R.S., Hait W.N. and Gallo M. PC-SPES and Prostate Cancer, (Letter). N Engl J. Med 340:568, 1999.

Medina P.J., DiPaola R.S., Goodin S. Treatment of Hormone Refractory Prostate Cancer. J Oncol Pharm Pract 4(4), 1998.

DiPaola R.S., Aisner J. Overcoming bcl-2 and p53 mediated resistance in Prostate Cancer. Sem of Oncol, 26: 112-116, 1999.

DiPaola R.S., Rafi M., Vyas V., Gupta E., Toppmeyer D., Rubin E., Patel G., Goodin S., Medina P., Zamek R., Zhang C., White E., Hait W.N. Phase I clinical and pharmacologic study of 13-cis retinoic acid, alpha interferon and paclitaxel in patients with prostate cancer and other advanced malignancies. J Clin Oncol 17:2213-2218, 1999.

DiPaola, R.S and Schuchter L. Neuroprotection by Amifostine. Seminars of Oncology 26, Suppl 7:82-88, 1999.

DiPaola, R.S. Approaches to the treatment of patients with hormone sensitive prostate cancer. Seminars of Oncology 26:24-27, 1999.

Cvijic M.E., Kita T., Shih W., DiPaola R.S., and Chin K.V. Extracellular Catalytic Subunit Activity of the cAMP-Dependent Protein Kinase in Prostate Cancer. Clin Cancer Research, 2000.

Rafi M.M., Rosen R.T., Vassil A., Ho C., Zhang H., Ghai G., Lambert G., Hait W.N., DiPaola R.S. Modulation of bcl-2 and Cytotoxicity by Licochalcone-A, a novel estrogenic flavonoid. Anticancer Research, 20:2653-2658, 2000.

Goodin S., DiPaola RS. Is there science for alternative medicine in prostate cancer? Highlights in Oncology Practice 18(3):72-76, 2000.

DiPaola R.S., P. Kumar, W.N. Hait, and R. Weiss. State of the Art Treatment and research in Prostate Cancer. New JerseyNJ Medicine, 2:23-34, 2001.

Nanquan Zhu, Rafi M.M., DiPaola R.S., Jingsong Xin, Chee-kok Chin, Vladimir Badmaev, Geetha Ghai, Rosen R., Chi-Tang Ho. Bioactive constituents from Gum Guggul (Commiphora wiightii). Phytochemistry 56:723-727, 2001.

Ankem MK, Hartanto VH, Han KR, Ferlise VJ, Bancila E, Cummings KB, DiPaola RS Metastatic renal cell carcinoma presenting as an oral tumor. Can J Urol 2001 Jun;8(3):1295-6.

Eid J.E., Brunner M., Segal L., Cummings K.B., Weiss R.E., Goodin S., Todd M., Aisner J., DiPaola R.S. Effect of P-30 Protein and Tamoxifen on TGF-Beta1 and IGF-1 in Patients with Prostate Cancer, Urologic Oncology 6:243-247, 2001.

DiPaola RS, Chenven ES, Shih WJ, Lin Y, Amenta P, Goodin S, Shumate A, Rafi MM, Capanna T, Cardiella M, Cummings KB, Aisner J., Todd M. Mitoxantrone in patients with prostate specific antigen progression after local therapy for prostate cancer. Cancer. 2001 Oct 15;92(8):2065-71.

DiPaola R.S., Patel J., Rafi M.M. Targeting Apoptosis in Prostate Cancer. Hematology/Oncology Clinics of North America. 15:3:509-524, 2001.

Zhu Nanqun, Kikuzaki H, Sheng S, Rafi MM, Nakatani N, DiPaola RS, Ghai G, Rosen R, Ho CT. Furanosesquiterpenoids of Commiphora Myrrh. J Nat Prod. 2001 Nov;64(11):1460-2.

Rafi MM, Vastano BC, Ho C-T, Ghai G, Rosen RT, and DiPaola RS. Novel polyphenol molecule isolated from licorice root (glycrrhiza glabra) induces apoptosis, G2/M cell cycle arrest, and bcl-2 phosphorylation in tumor cell lines. J. Agric and Food Chemistry 50:677-684, 2002.

DiPaola RS, Rinehart J, Nemunaiti J, Effinghaus S, Rubin E, Capanna T, Ciardella M, Fontaine M, Adams N, Williams A, Schwartz M, Winchell G, Wickersham K, Deutsch P, Yao S. Characterization of a novel prostate specific antigen activated peptide-doxorubicin conjugate in patients with prostate cancer. J Clin Oncol. 2002 Apr 1;20(7):1874-1879.

Morris M, Tong WP, Cordon-Cardo C, Drobnjak M, Kelly WK, Slovin S, Terry KL, DiPaola RS, Rafi MM, Rosen N, Scher HI. A phase I trial of G3139, a bcl-2 antisense drug, by continuous infusion as a single agent and with weekly taxol Clin Cancer Res. 2002 Mar;8(3):679-83.

S. Goodin, K. Rao, and R.S. DiPaola. State of the Art Therapies in Prostate Cancer. Oncologist 360-70, 2002.

Marks L, DiPaola R, Nelson P et al. PC-SPES: herbal formulation for prostate cancer. Urology 369-70, 2002.

DiPaola RS. To Arrest or not G2-M cell cycle arrest. The Biology Behind. Clin Cancer Res, 3311-4, 2002.

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DiPaola, R. Durivage, H. and Kamen, B. High time for low-dose prospective clinical trials. Cancer, 98: 1559-1561, 2003.

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Strair, R. K., Schaar, D., Medina, D., Todd, M. B., Aisner, J., DiPaola, R. S., Manago, J., Knox, B., Jenkinson, A., Senzon, R., Baker, C., Liesel, D., Ciardella, M., Kuriyan, M., Rubin, A., and Lattime, E. C. Antineoplastic effects of partially HLA-matched irradiated blood mononuclear cells in patients with renal cell carcinoma. J Clin Oncol, 21: 3785-3791, 2003.Thalislia, S. Goodin, E. Rubin, R.S. DiPaola. A phase I study of 13cis retinoic acid, interferon and weekly paclitaxel in advanced malignancies. Ca Chem and Pharm August, 2003.

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SUMMARY 1

CANCER CENTER RESEARCH PROGRAMS, PROGRAM LEADERS AND INVESTIGATORS: ACADEMIC TITLES AND DEPARTMENT AFFILIATIONS OF CENTER MEMBERS

WE need to fix FORMAT of table for program leaders (I could not figure out how to do this)

CODE: 067	**RESEARCH PROGRAM TITLE: Prostate CancerProgram**		
NAME	**UNIVERSITY ACADEMIC TITLE**	**UNIVERSITY DEPARTMENT AFFILIATION**	**TYPE OF MEMBERSHIP IN CANCER CENTER**
Program Leader: **Program Leaders:** Cory Abate-Shen, Cory, Ph.D.	Professor/Division Chief	RWJMS/ Neuroscience and Cell Biology Medicine/CABM	Full
Program Co-Leader: Robert DiPaola, Robert, M.D.	Associate Professor	RWJMS /Medicine/CINJ	Full
Program Members:			
Copeland, Paul, Ph.D.	Assistant Professor	RWJMS Molecular Genetics, Microbiology and Immunology	Full
DiBiase, Steven, M.D.	Associate Professor	RWJMS Radiation Oncology	Full
Fondell, Joseph, Ph.D.	Assistant Professor	RWJMS / Physiology and Biophysics	Full
Foty, Ramsey, Ph.D.	Assistant Professor	RWJMS /Surgery	Full
Hait, William N., M.D., Ph.D.	Professor	RWJMS Medicine and	Full

		Pharmacology	
Heck, Diane, Ph.D.	Assistant Professor	RU Pharmacology and Toxicology	Full
Hu, Longqin, Ph.D.	Assistant Professor	RU Pharmaceutical Chemistry	Full
Laskin, Jeffrey, Ph.D.	Professor	RWJMS/ Environmental and Community Medicine	Full
Morton,Jr., Ronald, M.D.	Associate Professor	RWJMS/ Surgery	Full
Pintar, John, Ph.D.	Professor	RWJMS /Neuroscience and Cell Biology	Full
Rabson, Arnold B., M.D.	Professor	RWJMS / Molecular Genetics, Microbiology and Immunology	Full
Reinberg, Danny, Ph.D.	Distinguished Professor/Division Chief	RWJMS /Biochemistry	Full
Roth, Monica, Ph.D.	Professor	RWJMS /Biochemistry	Full
Sarvazyan, Armen, Ph.D.	Adjunct Professor	RWJMS Surgery	Full
Shen, Michael, Ph.D.	Associate Professor	RWJMS /Pediatrics	Full
Todd, Mary B., D.O.	Associate Professor	RWJMS /Medicine	Full
Weiss, Robert, M.D.	Associateistant Professor	RWJMS /Surgery	Full

NOTES – is YAO an associate – should she be listed here??

Rabson strongly suggested we remove TSAI – I agree

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(we need to give the program members one final look when we are done)

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1. Overall Description

The Prostate Program is comprised of 16 15 investigators from 8 departments of RU and RWJMS; nine eight of these investigators are full members exclusively in the Prostate Program. Since its inception in 2001, members of the program have authored XXX peer-reviewed manuscripts or reviews, 1 book, XX abstracts, filed or received XXX patents, and obtained XXX federally funded grants. These grants include one from the NCI Mouse Models of Human Cancer Consortium, which has recently been given a high priority for renewal. Under the leadership of Drs. Abate-Shen and DiPaola, the program has promoted crossinter-disciplinary collaborations through its research meetings, retreats, symposia, and workshops.

The Prostate Program was established as a result of strategic planning and evaluation activities conducted by the CINJ Internal and External Advisory Boards following the last CCSG renewal. Drs. Arnold Rabson, Michael Reiss, and Joseph Aisner, Associate Directors for Basic, Translational and Clinical Science worked to initiate disease-based programs to promote interdisciplinary interactions and translational results.

The newly-established Prostate Program attracts both junior and senior investigators to pursue research in prostate cancer. Importantly, the monthly program meetings and symposia led to the idea for a Program Project application on Modeling Advanced Prostate Cancer to be submitted to NCI for February, 2004 (for details see section 6.1). Members of the Prostate Program were selected based on: (1) their interest in interdisciplinary research in prostate cancer; (2) their effectiveness as collaborators and willingness to work with other members of the Prostate Program and other CINJ programs; and (3) their demonstrated expertise and desire to focus on prostate cancer research, as evidenced by successful grant funding and peer-reviewed publications.

The last grant period witnessed the rapid maturation of prostate cancer research at CINJ, which is largely a reflection of the remarkable evolution in focus of program members who had previously exclusively been studying more fundamental aspects of cancer biology. Several of the members of the Prostate Program were previously pursuing basic mechanisms of transcriptional regulation and were formerly solely members of the Transcriptional Mechanisms and Oncogenesis Program. Today, these members help form this multidisciplinary research program that is striving to lead the field of prostate cancer research.

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This shift in focus, in conjunction with advice from internal and external advisors as well as progress reviews, led CINJ to launch this new disease-based program.

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The newly-established Prostate Program has attracted both junior and established investigators to pursue research in prostate cancer. Importantly, the monthly program meetings and symposia lead to the idea for a Program Project application on Modeling Advanced Prostate Cancer to be submitted to NCI for February, 2004 (for details see section XX). In the past year, program meetings and workshops have primarily revolved around the submission of this application, which involves several members of the Prostate Program.

Members of the Prostate Program were selected based on: (1) their interest in cross-disciplinary research in prostate cancer; (2) their effectiveness as collaborators and willingness to work with other members of the Prostate Program and other CINJ programs; and (3) their demonstrated expertise and desire to focus on prostate cancer research, as evidenced by successful grant funding and peer-reviewed publications.

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that will also lead to more effective strategies for prevention

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including studies that have been developed on the national level

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. Efforts have now begun to translate laboratory studies of oncogenesis into clinical studies of early detection and chemoprevention.

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underlying

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oncogenesis

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3. Cancer Focus/Rationale

Prostate cancer is the most common non-cutaneous malignancy afflicting men in the United States. Furthermore, for reasons that remain uncertain, this form of cancer has a peculiar predilection for African Americans. Since the incidence of prostate cancer increases with age, the significance of prostate cancer will continue to increase aging is an important risk factor for prostate cancer, as Americans enjoy longer lives, the significance of prostate cancer will continue to increase. The availability of Asensitives effective methods of for screening have become available, theincreased the frequency of diagnoses has transiently increased, leading to an explosion of utilization of surgical, radiation, and systemic treatments. Coupled with the discovery of many new systemic agentspotential new drug targets, the need for interactions between laboratory, clinical and population researchers and a multidisciplinary clinical research team to develop agents earlier in disease has never been more pressing. Furthermore, as a higher percentage of population gets older and thereby more susceptible to prostate cancer, there is a greater need for new strategies for prevention. Thus, the rationale for the development of this new CINJ program is to establish a multidisciplinary team of researchers with diverse scientific expertise to comprehensively address this pressing cancer problem.

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. Notably, several of the investigators whose work is described herein have recently made the transition to studying prostate cancer as a result of their interactions with program leaders

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has been

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chemotherapy

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development		
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the m		
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identified *Nkx3.1* as a prostate-restricted gene,		
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,		
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as well as		
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prostatic		
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have		
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long-standing interest		
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(Ding et al., 1998; Iratni et al., 2002; Schier and Shen, 2000; Yan et al., 1999)		
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(Bhatia-Gaur et al., 1999)		
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Dr. Shen		
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Members also investigate the role of		
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signaling for prostate cancer. Dr.		
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is another member who has been stimulated by the Prostate Program to expand his research interests from fundamental developmental biology to the study of prostate cancer. Dr.

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studies		
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, Pintar embarked on studies		
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which have been made available		
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Dr.		
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to our		
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institution as well as		
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He used these cell lines		

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that associate with AR and that are likely to mediate

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its

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tissue

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cells

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cells

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~~To further strengthen the Prostate Program's expertise in AR signaling, program leaders recruited **Dr. Chih-Cheng Tsai**. Dr. Tsai's early work identified and characterized a Drosophila transcriptional co-repressor, called SMRTER (Tsai et al., 1999). SMRTER is a Drosophila cognate of vertebrate SMRT (Silencing Mediator of Retinoic and Thyroid hormone Receptor) and N-CoR (Nuclear receptor Co-Repressor), which are known to bind the AR in an antagonist-dependent fashion. His recent research indicated that many of the known properties of AR, including its hormone-dependent nuclear localization, transcriptional activation, and chromosomal binding can be recapitulated in flies. Taking advantage of the observation that ectopic expression of AR in Drosophila eyes perturbs eye morphogenesis, Dr.Tsai will examine how this AR mediated eye phenotype can be modulated by mutations, by hormones agonists and antagonists, and by mutations corresponding to various nuclear receptor co-activators, co-repressors, chromatin remodeling factors, and histone modifying factors. This *in vivo* approach is expected to yield further insights into the biological and transcriptional properties of androgen receptor, and is an excellent complement to Dr. Fondell's studies.~~

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(Kuzmichev et al., 2002; Nishioka et al., 2002a; Nishioka et al., 2002b)

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Rabson feels strongly that we should delete TSAI

Dr. Danny Reinberg has recently embarked on prostate cancer research through his analyses of factors that alter chromatin structure to regulate gene expression (Kuzmichev et al., 2002; Nishioka et al., 2002a; Nishioka et al., 2002b). They isolated one such factor from Hela cells, which they termed PRC2, and found that it methylated lysine-27 on the histone H3 tail. They further showed that the enzymatic activity of PRC2 resides in a polypeptide termed Enhancer of Zeste (Ezh2). Ezh2, like most other histone lysine methyltransferases (HKMTs), contains a SET domain, which is an evolutionarily conserved sequence motif identified in the *Drosophila* PEV (position effect variegation) suppressor SU(VAR)3-9, the *Polycomb*-group protein Enhancer of Zeste, and the *trithorax*-group protein Trithorax. Work by Reinberg and other groups demonstrated that this class of proteins establish a restrained state of transcriptional repression during development, whereas perturbations of this system can have profound consequences for cancer cells. In particular, Dr. Reinberg

became interested in the potential role of Ezh2 in prostate cancer based on studies reported by others in which gene expression profiling of prostate cancer revealed a correlation of Ezh2 expression and the development of prostate cancer. He is collaborating with Dr. Shen to develop mutant mouse models for Ezh2 to investigate its role in the development of prostate cancer. Dr. Reinberg, working in collaboration with Dr. Abate-Shen, has recently shown that Ezh2 overexpression is inversely correlated with methylation of lysine-27 in prostate tissues, which has important implications regarding the mechanisms by which Ezh2 overexpression contributes to prostate cancer. Dr. Reinberg is one of the lead investigators on the Program Project Application on Advanced Prostate Cancer that will be submitted to NCI for February 1 (see Section X for details).

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pathological effects

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and activation of several genes known to promote growth and longevity

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Dr. Arnold Rabson, who is the Leader of the Transcriptional Regulation and Oncogenesis Program (TROP), is also an active and productive member of the Prostate Program because of his interest in this disease. Given his role as Associate Director for Basic Science, Dr. Rabson played an important leadership role in the genesis of disease-based programs in general and the Prostate Program in particular, which evolved in part through the "differentiation" of TROP members into prostate-cancer focused investigators. Dr.

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support his work on the Role of NF–κB in prostate cancer (Suh et al., 2002)

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Dr.

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Dr.

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NFκB

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working

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has

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One technique is

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measure properties of prostatic tissue including

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(Ryan et al., *Proc Natl Acad Sci U S A,* 2001; Duguay et al., *Dev Biol,* 2003; Robinson et al., *J Cell Sci,* 2003)(Duguay et al., 2003; Robinson et al., 2003; Ryan et al., 2001)

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used this approach to

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tissue surface tensiometry

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the

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prostate

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genes to be delivered to tumor cells

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Dr.

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Dr. Roth's approach

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takes

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they

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productively

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targeted

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cancer

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(Abate-Shen, 2002; Abate-Shen et al., 2003; Abate-Shen and Shen, 2000; Abate-Shen and Shen, 2002; Bhatia-Gaur et al., 1999; Kim et al., 2002a; Kim et al., 2002b)

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recently renewed

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to Dr. Abate-Shen

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, which has recently been given a high priority for renewal

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(Bhatia-Gaur et al., 1999; Kim et al., 2002a)

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(Abate-Shen et al., 2003; Kim et al., 2002b)

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To help with these types of studies, Dr. Michael

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To facilitate imaging studies of mouse models, Abate-Shen and Shen have contributed to a NCI SAIRP grant on small animal imaging, which was submitted in December, 2003

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pursue more focused studies on

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overexpression

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, flutamide and

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hydroxyflutamide. An ~~critically~~ important observation was that

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was not affected by p53/MRP [what does this mean – does it mean mutation of –53?]. Consequently,

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do

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[this sounds too strong – how about " androgens are effective for signaling through their receptors but anti-androgens did not.]

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suggested

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results. [how about "more effective outcomes".]

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Drs.

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(Cancer Pharmacol/Developmental Therapeutics)

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~~yet~~

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(D0),

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testing the hypothesis that treatment of agents early prior to the development of mechanisms of resistance will improve outcome. These studies also assessed molecular mechanisms of resistance in patient's correlates, as shown in the early stage D0 studies summarized in Table 2

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Despite lower expression levels of markers of resistance, the

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. Examples of investigator-initiated studies completed fore early disease are listed in Table 2. [Is early disease chemoprevention – I do not think so but just checking.]

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Based on these data s

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agents, or

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, were also conducted.

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In addition to the progressive increase in expression of drug resistance genes observed by the Hait laboratory, several

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In collaboration with **Dr. Arnold Levine** (Molecular Mechanisms of Tumor Growth), this team

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and **Hait**		
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Dr. DiPaola		
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(a MAP4-targeting agent)		
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[will this be defined before?] using epothilone as salvage therapy		
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In addition to these studies members of the prostate program are developing novel strategies for chemotherapy. For example, **Dr. Lonqin Hu** has been utilizing synthetic medicinal chemistry and bioorganic chemistry to design to anticancer prodrugs that target these enzymes in advanced prostate cancer. Currently, they are targeting signaling pathways that are utilized by protein serine/threonine kinases. They have designed a series of proactive that are designed to be activated site-specifically in tumor tissues. Their approach utilizes mechanism and inhibition of enzyme action to target the relevant pathways.

The translational research arm of the Prostate Program has emphasized the significance of investigator initiated clinical trials, as highlighted for various points in the progression of prostate cancer in Table 2. In addition, program members are active participants in ECOG and intergroup trials, as well as cooperative efforts with other cancer centers. This work is promulgated by the recent appointment of Dr. DiPaola as co-Chair of the ECOG Genitourinary Committee. In this administrative role, Dr. DiPaola is responsible for the development of studies within the committee, as well as serving as principal investigator in a number of studies. Approved developing studies (in addition to those shown in Table 2) that Dr. DiPaola will serve as principal investigator include the use of epothilone as a salvage therapy in prostate cancer and a randomized phase III study of prostvac vaccine in combination with GM-CSF in patients with PSA progression after local therapy. The later study is based on prior data on a vaccine trial in ECOG, for which Dr. DiPaola acted as co-PI, demonstrating that the most optimal vaccine schedule was a prime and boost approach (E7897, ASCO 2002, Manuscript submitted).

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anticipate continued growth in the translational research program during the next grant period. Investigators in the program have clearly demonstrated the productivity and efficiency of pursuing investigator- initiated studies directed towards different stages in the prostate cancer progression, as shown in Table 2, which are based on studies from the laboratory. The tremendous expansion of the translational research program, as evident from the extensive list of investigator initiated trials listed in Table 2, emphasizes the need to expand clinical investigations, especially those with focused on early disease, and prevention. To achieve these goals the Cancer Institute leadership has been successful in the recruitment of an internationally-recognized senior urologist, Dr. Ron Morton, who will head the CINJ Urologic Oncology Division and the Division of Urology at RWJMS Chief of Urologic Oncology. ~~The pace of work will now be accelerated with the arrival of Dr. Ron Morton.~~ [redundant with previous sentence]

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~~in mice and men~~

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Scientifically, members will

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recently developed

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cancer control effort

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through the combined efforts of multidisciplinary teams of basic, clinical, and population scientists.

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studies based in

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, have led to investigator-initiated clinical trials

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These studies are complimented by clinical efforts aimed at identifying effective screening strategies.

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Finaslly, these efforts have been bolstered by t

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such as carcinoma of the breast and prostate.

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a platform

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and serves as a natural interface with the Carcinogenesis and Chemoprevention and Cancer Control Programs.

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based on their identification of

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novel

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nutrients

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,

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which is a protein that oxidized prostate

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of the oxidase have been obtained and

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cells

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ing the cDNA

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characterized. They identified Four

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. Thus, by inhibiting this highly specific target and blocking the activation of prostate carcinogens, nutrients display chemopreventative activity. In collaboration with Dr. Michael Gallo (Carcinogenesis and Chemoprevention), they also investigated the effects of anti-estrogens on cytochrome P450 mediated metabolism of prostate carcinogens. Anti-estrogens, which include some dietary nutrients, modulate expression of the P450 enzymes. Natural products that suppress oxidative damage in prostate tissues and prevent carcinogen metabolism have the potential to suppress the initiation and progression stages of prostate carcinogenesis in humans. During the next grant period, collaborative efforts are planned to validate this target in mouse models and in human prostate cancer, and program members will initiate clinical trials with dietary nutrients to assess the development and progression of prostate cancer.

Dr.

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has

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obtained recent RO1

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In 1996, it was reported that d

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supplementation resulted in a significant

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reduction in

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increased

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(Copeland, C., *Annu Rev Nutr*, 2003)

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provide a

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barrier

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to cellular components, including DNA

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Copeland

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has focused on the idea

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a significant part of

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the result of

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are likely to

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It is therefore of great importance to determine whether selenoprotein synthesis is a central part of the protective action of selenium, and thus a study of the regulation of this process is a critical part of discovering the mechanism of selenium chemoprevention.

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cadmium-induced carcinogenesis of normal

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cells in culture. In addition, to address the regulation of selenoprotein synthesis during prostate oncogenesis, he will identify the point of regulation responsible for the dramatic down-regulation of selenoproteins in prostate cancer as well as determine the contribution of the selenocysteine incorporation machinery to this regulation.

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of this research

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Program members have been pursuing several investigator-based clinical trials aimed at chemoprevention (Table 2). Investigators in the program have been investigating the possibility that alterations in hormonal signaling may provide new methods of chemoprevention. In particular, hormonal therapy has been the mainstay for treatment of early metastatic prostate cancer since Beatson demonstrated the beneficial effects of orchiectomy. Despite enormous benefits in terms of palliation, few if any patients are cured with this form of treatment. Program members explore basic mechanism of androgen action with the goal of understanding how cells escape from androgen dependence (**see 4.1; Fondell.**). At the same time, program members have been exploring novel hormonal treatments that have yielded unanticipated results. For example, **Drs. DiPaola, Hait, Gallo** (Carcinogenesis and Chemoprevention) and **Lambert** (Carcinogenesis and Chemoprevention) described the biological actions and toxic side effects of PC-SPES

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Based on these data demonstrating the importance of further study of novel estrogens, Drs.

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have intiated

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initiated studies of

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Pilot

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hormone and chemo-refractory

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multiple

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herbs such as

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which has been patented by the group

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DHP

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in

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models

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of the androgen receptor by

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Dr.

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what program

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), as an interprogramatic collaboration,

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was found to fit in the binding pocket with with the androgen receptor in a configuration consistent with an antagonist

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, and consistent as an estrogen receptor agonist.

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currently preparing

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submission as a collaboration

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study this agent further

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capable of both antiandrogen receptor antagonisms and estrogen receptor agonist activity.

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models

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Drs. DiPaola

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Abate-Shen

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mouse

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models

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delivery to mice that are predisposed to prostate cancer mice

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DESCRIPTION (provided by applicant): Prostate cancer is the most common solid malignancy in men and the second most common cause of male cancer-specific mortality. Over the past fifteen years, the implementation of testing for prostate specific antigen (PSA) has revolutionized the diagnosis and treatment of this important disease. Moreover, emerging epidemiologic evidence suggests that the prostate cancer mortality rate is decreasing directly due to PSA screening. Current PSA testing methods remain both inconvenient and costly when applied to screening. Conservative estimates place the projected cost of PSA testing for screening purposes alone at greater than three billion dollars a year in the United States. These characteristics impact particularly on the population of low-income patients at high risk for prostate cancer who may be uninsured or live in underserved areas. We have designed a prototype biosensor chip for quantitating blood PSA levels. This chip is an amperometric immunosensor, which would form the core of an inexpensive handheld device for measuring PSA at the bedside or in the physician's office. A critical goal of this project will be to produce a fusion molecule that shares PSA immunoreactivity and glucose oxidase enzymatic activity. This conjugate molecule will compete with PSA at the chip surface and thereby couple immune recognition to an easily detectable electrical signal. A device of this type should significantly impact the diagnosis and treatment of prostate cancer by lowering the cost and broadening the availability of PSA testing for all patients at risk. This is of particular concern given the striking racial differences in prostate cancer mortality, which may be attributable to inadequate access to PSA screening in medically underserved populations.

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, a highly effective prostate cancer advocate

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5. Value Added

5.1. Value Added by the Center to the Program

CINJ adds value to the Prostate Programits programs by providing centralized shared resources, strong program leadership, and effective mechanisms to promote interprogrammatic collaborations and translational research. Some of these, as they pertain to the Prostate Program, are summarized as follows:

Shared Resources: Every member of the Prostate Program uses CINJ shared resources. The most heavily used include the new Transgenic/knockout Core, DNA Sequencing, Analytical Cytometry/Image Analysis, Immunohistochemistry, Tissue Retrieval Service, Biometrics, Research Pharmacy, and the Office of Human Research Services. A brief summary of usage is provided below:

Transgenic/knockout core: Under the direction of Michael Shen, a member of the Prostate Program, this facility has been instrumental in developing most of the mouse models of prostate cancer described in this section. The core is heavily utilized by Drs. Cory Abate-Shen, Danny Reinberg, and Joseph Fondell, and is a vital component of the Program Project Application that has been submitted by these investigators.

Biometrics: The Biometrics Shared Resource provides several essential components of support for Program members. This shared resource participates in the planning of all clinical trials, prior tbeforeo review by the

Scientific Review Board. In addition, the pre-clinical studies in mouse models also require the expertise of Dr. Weichung Joe Shi (Resource Manager) and colleagues for their appropriate design and implementation; Dr. Shih is a partipantparticipant in the program project application submitted by members of the prostate program. The Biometrics resource also provides essential advice and statistical support for the microarray studies that are being pursued by members of the program; these efforts have lead to the submission of an AACR abstract and manuscript in collaboration with Drs. Abate-Shen and Shen.

DNA sequencingSequencing: This core is extensively used for DNA sequencing by program members who do molecular biology research, including FFondell, Hait, Laskin, Reinberg, Roth, and Shen.

Analytical Cytometry/Image AnalysisFlow Cytometry: Investigators utilizing cell culture model systems, including Drs. Abate-Shen, DiPaola, Fondell, Hait, Reinberg, Fondell and Laskin, utilize the flow cytometry core for cell analysis and sorting. The cell sortingThis facility has been utilized in several manuscripts published by program members (e.g., (Kim et al., 2002b)). Recently, Dr. Shen has been using this resource in their efforts to isolate prostate stem cells and cancer stem cells.

Microarray facilityTranscriptional Profiling: This core facility is used by program members in theirto analyzeses of prostate tumors from the mutant mouse models by gene expression profiling by Abate-Shen and Shen.. The availability of mutant mice that recapitulate all stages of prostate carcinogenesis has provided a unique opportunity to survey gene expression changes that distinguish these various disease stages. With the assistance of the microarray core, members of the prostate program are now performing microarray gene profiling of the mutant prostate tissues. Their goal is to achieve comprehensive analyses of the gene expression changes that distinguish the various stages of prostate cancer in the mouse, which will then be compared with analogous studies to changes in human prostate cancer. Members including DiPaola and Hait use the facility for profiling of human tissues obtained for clinical and translational research and laboratory correlates of clinical trials.
The advantage of pursuing these studies using the mutant mice is the unique opportunity to survey all disease stages, some of which are relatively inaccessible in humans.

Tissue Retrieval Service: Numerous investigators rely on the Tissue Retrieval Service TRS for fresh and preserved tissues. Rabson, Hait, DiPaola, Chada and others have received literally hundreds of prostate specimens for their research. In addition, the TRS Tissue Retrieval Service provides support for all clinical trials in which tissues are required for correlative studies.

Immunohistochemistry: This shared resource provides support for all studies requiring immunohistochemical analyses. They specifically have worked with Rabson in his analyses of NF-κB expression in prostate cancer, and Hait in his analysis of drug resistance proteins in archived specimens. DiPaola, Hait and Todd use this resource extensively for laboratory correlates of clinical trials.

Tissue Microarray: This newly established shared resource recently produced a prostate tissue microarray that will be used extensively by program members during the next grant period.

Laboratory Support Services: The Laboratory Support Services LSS provides essential laboratory support for all program members housed in the CINJ building in New Brunswick including DiPaola, Hait, and Mortonand others.

Office of Human Research Services: This shared resource is used by all members involved in clinical and population trials involving human subjects.

Research Pharmacy: This shared resource is used by all members involved in clinical research and prevention trials requiring administration of any agent to a human subject (e.g. PC-SPES). Dr. DiPaola

worked closely with Dr. Goodin (Resource Manager) to …assure proper documentation, drug distrubution, and data collection on pharmaceutical and nutraceutical agents used in clinical trials.

Immunohistochemistry: This shared resource provides support for all studies requiring immunohistochemical analyses. They specifically have worked with Dr. Rabson in his analyses of NfkB expression in prostate cancer and Dr. Hait in his analysis of drug resistance proteins in archived specimens. In addition, they have produced a Prostate Tissue Array that will be used extensively in the program project application submitted by program members.

Program Leaders: Drs. Abate-Shen and DiPaola actively recruit members to pursue disease-focused research in prostate cancer. They identify potential collaborations, foster communication, organize monthly program meetings, seminars and workshops. They and set an example through their own collaborative, multidisciplinary research effortsactivities, which are multi-tiered and multi-disciplinary. The program leaders have beenare highly effective in recruiting junior and established senior investigators to initiate research projects in prostate cancer. Furthermore, they have become increasing sought after mentors for their prostate cancer expertise and help review new grant applications and manuscripts submissions. Their efforts have lead to the submission of a program project application (see below).

Monthly Scientific Council Meeting: Drs. Abate-Shen and DiPaola attend represent the Prostate Program membership at the Scientific Council meetings., serving as liaisons between the members and the IAB and acting in the interests of program members. Each month, a member of a program is chosen by one of the program leaders to present a 30-minute seminar on work in progress. The members of the Scientific Council include the program leaders and the shared research managers. These individuals evaluate the presentation with the goal of developing interprogrammatic collaborations and finding opportunities for translational research. The monthly Scientific Council meetings also encourage the development of joint training programs, program projects, relevant new graduate courses, and seminar programs.

Developmental Funds: CINJ leveraged CCSG Developmental funds with the work of Ms. Betty Gallo and the CINJ Development Office to provide support

for pilot projects. During the last grant period, the following Pilot grant were awarded:

Table 4. • Use of Developmental Funds for Pilot Projects

PRINCIPAL INVESTIGATOR	PROJECT
K.V. Chin, $25,000 (Pilot Project)	Profiling Gene Expression Patterns in Prostate Cancer
Stuart Lutzker, Pilot, $80,000 (Pilot Project)	Abrogation of the mitotic spindle-checkpoint in prostate cancer cells and sensitivity to antimicrotubule drugs
John Pintar, $65,000 (Pilot Project)	Genetic studies of IGFBP function during prostate tumorigenesis
Arnold Rabson, $80,000 (Pilot Project)	Role of NF-kB in Prostate Cancer
Robert Weiss, $19,900 (Pilot Project)	Presence of green tea in the prostate
Longqin Hu, $25,000 (Pilot Project)	Alkylating agents to target site-specifically slow-growing prostate cancer cells
Allan Conney, $60,000 (Pilot Project)	Effect of 12-0-tetradecanoylphorbol-13-acetate (TPA) on the growth of prostate tumors
Pintar, $60,000 (Pilot Project)	Genetic studies of IGEBP function during prostate tumorigenesis
Carlos Molina. $30,000 (Pilot Project)	Regulation of the putative tumor suppressor ICEr in prostate cancer by PTEN and P13K signaling

Advocacy/Development: Dean and Betty Gallo Prostate Center: One of the most successful CINJ initiatives involved the harnessing of the enormous energy, insights, and enthusiasm of prostate cancer advocates. In particular, Ms. Betty Gallo's efforts formed the Dean and Betty Gallo Prostate Cancer Center, a CINJ activity that raises public awareness and helps raise money to support pilot projects, outreach, and education activities. This funding has been used to help support many key initiatives of the Prostate Program, such as its pilot grant programs, Symposia and Workshops, and Research Working Group. The Gallo Center works with the 100 Black Men of New Jersey to conduct free education and screening to underserved communities throughout the state and the Men's Health Network to raise awareness throughout the nation. Through these community relations, new opportunities for screening and prevention will occur.
One of the successful CINJ initiatives has been the harnessing of advocates enthusiasm to raise funds to support prostate cancer research and outreach programs In particular, Ms. Betty Gallo's efforts formed the Dean and Betty Gallo Prostate Cancer Center, a CINJ development activity that has raised money to support pilot projects, outreach, and education activities. Ms. Gallo has effectively partnered with the 100 Black Men, a national advocacy group for African Americans, to raise community awareness of the dangers of undetected prostate cancer.

New Jersey Cancer Trials Connect (www.njctc.org): One of the most common reasons patients give for not participating in clinical trials that they were not informed about them. Dr. Susan Goodin led A this CINJ initiative with state government that culminated in New Jersey Cancer Trials Connect, a web-based clinical trials matching system designed to increase access to clinical trials available in the state (www.njctc.org). This unique platform allows individuals to log in and obtain a secure home page, through which they can enter key information about their diagnosis. The software then downloads clinical trials for which they are potentially eligible and relevant contact information. The website also provides up-to date information about each disease. Currently, NJCTC receives over 10,000 hits per day and over 1,000,000 visits since its launch in the Spring of 2003.

Access has been enhanced by efforts of Drs. Todd and DiPaola in establishing the CINJ Oncology Group, a statewide cooperative effort designed to foster accrual to clinical trials available on New Jersey Cancer Trials Connect. Dr. DiPaola is the leader of CINJOG and to date has activated 5 clinical trials through this mechanism. Dr. DiPaola works with Ms. Betty Gallo who particpates with the 100 Black Men organization to screen high-risk populations and provide the community with information on early detection and treatment

CINJ Oncology Group: As described in 4.4, CINJOG is a recently formed statewide cooperative effort to increase access and enhance accrual to clinical trials. Overseen by the Deputy Director, Dr. Todd, and directed by Drs. DiPaola and Goodin, CINJOG has held two retreats in 2003 to launch the effort, and opened 5 clinical trials. A centralized IRB was created for affiliate hospitals to open trials. It CINJOG continues withholds biannual meetings in which committees of various tumor types continue to develop a menu of trials. Additionally, a relationship has begun to form with industry to support CINJOG efforts. In year 2 and 3 the development of additional phase II studies and the start of phase III studies is planned.

Corporate Relations Committee: This subcommittee of the CINJ Board of Directors includes many leaders of the New Jersey Pharmaceutical industry. Through CRC activities, Prostate Program members have unique access to new compounds for early investigation and have access to industry scientists for collaborations.

Annual Scientific Retreat: The CINJ Annual Scientific Retreat is a consistently successful forum for the members of CINJ to review the latest research of CINJ members and peers from around the state. The abstract categories are organized by CINJ programmatic themes and grouped for presentation and discussion accordingly. Last year, over XXX participants presented over XXX papers. Last year, members of the program presented XXX posters and XXX oral presentations, several of which were collaborative. The 2002 retreat featured a Prostate Cancer symposium organized by Abate-Shen and DiPaola. Presentations included "Tissue

Recombinant Models of Prostate Carcinogenesis", Gerald R. Cunha, University of California San Francisco; "Clinical Progress in Prostate Cancer", Philip Kantoff, Dana-Farber Cancer Institute, and "Prostate Cancer: Precursor and Pathobiology", Angelo DeMarzo, Johns Hopkins University.

5.2. Value Added by the Program to the Scientific Members

The Prostate Cancer Program adds value to its members by: (1) providing opportunities for interactions that strengthen individual and programmatic research; (2) hosting external advisors to meet with program members, discuss research, and present research seminars; and and; (3) by awarding seed money for "high-risk" research ideas. of interest to the program as a whole as follows:

Monthly Program Meeting: The Prostate Program meeting allows investigators with varied scientific expertise to exchange informationhosts. multi-disciplinary research working groups, which provide a forum for scientific exchange and discussion, as well as an opportunity to learn about the research ongoing in the scientific community. Examples from recent meetings are provided below. These meeting have lead to the idea for a program project grant, which has been submitted by members of the Prostate Program (See below). Work-in-progress is presented and critiqued. The meeting is open to faculty and trainees, thereby providing a superb educational experience for young investigators with a potential interest in prostate cancer research.

---------- Page Break ----------

Retreats and Symposia: The Prostate Program has hosted two workshops, one symposia, and one program project retreat, which have engaged members of the community and have served as an opportunity to educate investigators on the status of prostate cancer research. The workshops and Symposia have included presentations from members within the community as well as well-known experts. The programs are listed in Appendix A. The most recent workshop, held on December 11, 2003, was focused on the program project application submitted to NCI, February, 2003.

Program-Specific Advisors: The Prostate Program obtains advice from prominent members of the research and advocacy community. Examples of individuals who have visited to help evaluate the plans and progress of the program include:

Gerald R. Cunha, Ph.D.
Professor
Department of Anatomy
University of California San Francisco

Robert J. Mayer, M.D.
Department of Adult Oncology
Dana Farber Cancer Institute

Margaret Foti, Ph.D.
Executive Director and Director of Publications
American Associate for Cancer Research

Peter Scardino, M.D.
Professor of Urology
Memorial Sloan Kettering

William B. Isaacs, Ph.D.
Associate Professor of Urology and Oncology
John Hopkins University

Keith Yamamoto, Ph.D.
Professor and Chairman
University of California San Francisco
Department of Pharmacology
San Francisco, CA 94143-0448

6. Collaborations

6.1. Intraprogrammatic Collaborations

The Prostate Program is made up of a highly interactive group of laboratory and clinical researchers, as has been alluded to throughout the description of the research accomplishments. Evidence of this collaborative nature is best exemplified by the fact that several program members have recently contributed to the submission the submission of a program project application on mechanisms of advanced prostate cancer. These members include Michael Shen, who is the PI, as well as Reinberg, Fondell, Abate-Shen, DiPaola, and Shi, who each contribute in various capacities. Other program members, including Hait and Rabson, serve on the internal advisory board. The four projects and the cores are:

Table 4. • Program Project Submitted by Prostate Program Members

MEMBER	PROJECT TITLE
Michael M. Shen, Ph.D. (PI)	*Analysis of metastatic disease in mouse models of prostate cancer*
Cory Abate-Shen, Ph.D.	*Modeling hormone-refractory prostate cancer in the mouse*
Danny Reinberg, Ph.D.	*Ezh2 and associated proteins in prostate cancer*
Joseph Fondell, Ph.D.	*Analysis of AR-interacting proteins and their role in hormone-dependent and independent transcriptional regulation*

Other examples of intraprogrammatic collaborations were highlighted in Section 4.0. are as follows:

Drs. Cory Abate-Shen and Michael Shen have a long-standing collaboration to study prostate development and cancer using mutant mouse models.

Drs. Cory Abate-Shen and Robert DiPaola have been collaborating to utilize these mouse models for pre-clinical studies. They now have trials set up for chemoprevention as well as chemotherapeutics.

Drs. Michael Shen and Danny Reinberg have a long-standing collaboration to examine the functions of transcriptional regulatory genes in mutant mice. They are now developing models to study the function of Ezh2 in prostate cancer.

Dr. Joseph Fondell is collaborating with Dr. Danny Reinberg to study the functional consequences of AR-protein complexes by chromatin immunoprecitation, using cell lines that have been developed in Cory Abate-Shen's laboratory.

Drs. Danny Reinberg and Cory Abate-Shen have been collaborating to study the expression of Ezh2 and other polycomb gene products in prostate cancer and metastases.

Dr. John Pintar has been collaborating with Dr. Cory Abate-Shen to generate combinatorial mutants of IGF-BP and *Nkx3.1* genes.

Dr. DiPaola is collaborating with Dr. Grace Lu-Yao (Cancer Control) on methods of determining proper use of screening tests and follow-up surveillance tools.

6.2. Interprogrammatic Collaborations

Disease-based programs were developed to enhance inter-disciplinary research and inter-programmatic collaborations. Some of the numerous interactions are summarized as follows:

DIVISION OF BASIC SCIENCE:
(I THINK THIS PARA IS TOO LONG – CAN WE CUT IT)

Dr. DiPaolaDiPaola collaborates with Dr. Edmund Lattime (Cytokines, Cytokine Signaling and Cancer) Growth Factors and Signal Transduction) to develop immunologic approaches to the treatments of prostate cancer. Dr. Lattime develops developed vaccinia-based vaccines and is a member of the developmental Developmental Ttherapeutics Committee of ECOG. The ECOG study E7897 was a randomized phase II trial that utilized several sequences of fowlpox- and vaccinia-derived vaccines directed against PSA developed written by Dr. DiPaolaDiPaola and Dr. Howard Kaufman at (Columbia University). The purpose of this trial was to evaluate the effect of this vaccine on biochemical PSA-progression and determine the effect on cellular immunity. Patients were randomly assigned to one of three treatment arms: (1) fowlpox-PSA vaccine alone every 6 weeks for 4 total vaccinations, (2) three vaccinations with fowlpox-PSA vaccine followed by one vaccination with vaccinia-PSA vaccine, or (3) vaccinia-PSA vaccine followed by three vaccinations with fowlpox-PSA vaccine. Sixty-four patients were treated over 12 months, and preliminary results were recently reported (*ASCO Proceedings*, 2002, Manuscript submitted). Eighty percent of patients had stable disease while on study, and median time to progression of 14.7 months. Increased PSA specific T-cell immunity was also demonstrated in 50% of the patients assessed, as shown in figure 2. These data demonstrate the safety of this therapy in the cooperative group setting and supported the use of the prime boost arm for future studies. Dr. DiPaolaDiPaola recently completed a study to determine if the cellular immune response to vaccinia-based vaccines would be improved with the addition of co-stimulatory molecules (TRICOM). A phase I study with the prime boost approach with TRICOM was recently completed 4/03. The study demonstrated safety of the approach. Planned studies now include E9802, a phase II randomized study of pox PSA Vaccine and TRICOM with and without GM-CSF in patients with stage D0 prostate cancer.

Drs. DiPaola, Hait, Levine and Eileen White (Molecular Mechanisms of Tumor Growth) collaborate on models of p53 and bcl-2 mediated resistance to guide the design of clinical trials. This collaboration has resulted in the development of the ECOG study of retinoic acid and interferon with paclitaxel (E3899) and the DOD funded RITE study using retinoic acid and interferon combined with estramustine and taxotere. Through funding by a pilot project grant, Dr. White and DiPaola have share a postdoctoral fellow in Dr. Whites laboratory to foster this collaboration.

Dr. Arnold Rabson collaborates with Dr. Celine Gelinas (Transcriptional Regulation of Oncogenesis) to studyon the consequences of NF–κB activation in the development of prostate cancer.

DiPaola and William Welsh (Cancer Pharmacology/Developmental Therapeutics) are collaborating on the computational discovery of novel AR antagonists and estrogen receptor agonists.

DiPaola and Rubin (Cancer Pharmacology/Developmental Therapeutics) collaborate on multiple studies that bridge the phase I group and Prostate Program.

DIVISION OF CLINICAL SCIENCE:

Monica Roth is collaborating with Joseph Bertino on customization of Env proteins for efficient gene delivery to hematopoietic stem cells.

Rabson is collaboration with Roger Strair (Cancer Pharmacology/Developmental Therapeutics) to design pharmacological measures to disrupt constituitive activation of NF-κB in leukemias and lymphoma.

Robert DiPaola collaborates with Toppmeyer (Breast Cancer Research) and Rubin (Cancer Pharmacology/Developmental Therapeutics) to inactivate bcl-2 mediated drug resistance in clinical trials.

Laskin, Shen, and Abate Shen collaborated with Banerjee to obtain RU institutional funds to purchase imaging instrumentation (Cancer Pharmacology/Developmental Therapeutics).

Cory Abate-Shen has recently shown that the homeobox gene *Msx-1*, is a key regulator of cyclin D1 mRNA expression. The question whether *Msx*-1 activation is responsible for cyclin D1 overexpression in breast cancer is being addressed in collaboration with the Reiss lab

Shen is collaborating with Reiss on the role of EGF-family members in the initiation and progression of breast cancer.

DIVISION OF PREVENTION, CONTROL AND POPULATION SCIENCE:

Dr. DiPaolaDiPaola collaborates with Dr. George Lambert (Carcinogenesis and Chemoprevention), Robert Rosen (Carcinogenesis and Chemoprevention), and Dr. Mike Gallo (Carcinogenesis and Chemoprevention) on multiple studies of herbal therapies that contain estrogens. Prior published collaborative studies have included PC-SPES and licorice root. Ongoing studies include the assessment of licorice root in men with prostate cancer and licorice root combined with taxotere chemotherapy (both funded by the NCI). Dr. William Welsh recently published data on computer modeling licorice root derivatives isolated by Drs DiPaola, Lambert, and Rosen demonstrating binding to the androgen receptor. (Welsh et al. Manuscript 2003)

Dr. Robert Weiss collaborates with Dr. C.S. Yang (Carcinogenesis and Chemoprevention) to assess the effects of green tea on men undergoing prostatectomy. Tissue is retrieved by the Tissue Retrieval Service and assessed for the detection of specific tea polyphenol compounds.

DiPaola, Hait, and A-N Kong (Carcinogenesis and Chemoprevention) are exploring the role of tmor necrosiss factor in androgen-independent prostate cancer.

Dr. Cory Abate-Shen is planning studies with CS Yang (Carcinogenesis and Chemoprevention) to assess the effects of green tea and other agents for the development of prostate cancer in mutant mouse models.

Dr. DiPaola and Dr. Welsh (Dept Pharm) are collaborating on the computational discovery of novel agents that are AR antagonists and estrogen receptor agonists.

Dr. DiPaola and Dr. Rubin (Pharm) have collaborated on multiple studies that bridge the phase I and prostate program, including a phase I study of retinoid/interferon (JCO1999, Ca Chemo Pharm 2003), and the study of a novel PSA activated doxorubicin peptide conjugate (JCO 2002).

7. Program Evolution and Future Development

7.1. Evolution

As part of the CINJ strategic plan to increase interdisciplinary cross-disciplinary interactions and translational research, two new disease- based programs were formed from the previous Clinical Investigations Program, and the Phase I Tumor Study Group was incorporated into the Cancer Pharmacology Program. . The Prostate Program drew on the strengths of members of the Genitourinary Tumor Study Group, lead by Dr. DiPaolaDiPaola, and the Transcriptional Regulation of Oncogenesis Program, lead by Dr. Abate-ShenRabson, to promote interdisciplinary research in prostate cancer. Through program meetings, workshops, and symposia, Drs. Abate-Shen and DiPaola have assembled a group of investigators with diverse backgrounds, many of whom were previously pursuing more fundamental aspects of cancer biology, into a dynamic, cohesive program. . The creation of thedevelopment of the Prostate Program has relied heavily on the developing Transgenic and Knockout core facilityMouse Shared Resource, that is now included as a full Shared Resource in this renewal. , which This facility has generated a majority of the unique mutant mouse lines that are described in the research accomplishments and will be essential for the future design of new approaches to

prevention and treatment. . These models have provided important new resources for studying mechanisms of prostate cancer, as well as effective pre-clinical models for testing new strategies for chemoprevention and chemotherapy (Table 1). Members of the Prostate Program has been aggressive in utilizinguse cell culture models to investigate new therapies, and have used these laboratory-based studies to launch an extensive series of investigator-initiated clinical trialss (Table 2). In addition, members of the prostate program are pursing basic, clinical and translational studies for chemoprevention and cancer control. ; Ttherefore, we anticipate that the Prostate Program will provide an increasingly powerful and effective platform for CINJ cancer control activities in collaboration with the programs of the Division of Prevention, Control, and Population Science.. Final

ly, the effectiveness of the Program leadership and the commitment of Program members is exemplified by their submission of a program project application to NCI.

To date, members benefited tremendously from the establishment of the Dean and Betty Gallo Prostate Cancer Center. This CINJ Center was founded as a result of powerful advocacy efforts led by Mrs. Betty Gallo, wife of Congressman Dean Gallo, who succumbed to prostate cancer. Ms. Gallo raises money and awareness through her tireless efforts. This funding has been used to support many key initiatives of the Prostate Program, such as its pilot grant programs, Symposia and Workshops, and Research Working Group. In turn, her efforts produced a vital means of establishing a cohesive research community and helping investigators to develop far-reaching collaborations.

7.2.

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Prostate biopsies in men with limited life expectancy.

Wasson JH, Bubolz TA, Yao GL, Barry MJ.
Center for the Aging, Dartmouth Medical School, Hanover, NH 03755-3862, USA.
john.h.wasson@dartmouth.edu

CONTEXT: Authorities discourage prostate screening in men who are likely to die from causes other than prostate cancer. PRACTICE PATTERN EXAMINED: Use of prostate biopsy-a proxy for screening-in men aged 65 and older with limited life expectancy (i.e., estimated to be less than 10 years). DATA SOURCE: Five percent samples of Part A (hospital) and Part B (physician) Medicare claims for 1993 through 1997. RESULTS: 22% of all Medicare beneficiaries who underwent a prostate biopsy had a limited life expectancy, corresponding to a rate of 1420 biopsies per 100,000. This rate did not change significantly between 1993 and

1997. For men with a life expectancy greater than 10 years, the biopsy rate was 2,360 per 100,000. Among men with limited life expectancy, in the year following the biopsy, 1.6% had radical prostatectomy and 2.3% had external-beam radiation. Thirty-nine percent were hospitalized. CONCLUSION: A substantial proportion of prostate biopsies are being performed in men with a life expectancy of less than 10 years. These men are unlikely to benefit from the biopsy or subsequent treatment. Semin

Oncol. 2003 Jun;30(3):390-400. Related Articles, Links

An evidence-based approach to prostate cancer follow-up.
Yao SL, Dipaola RS.
Cancer Institute of New Jersey, The Dean and Betty Gallo Prostate Cancer Center, New Brunswick, NJ 08901, USA.
The follow-up required for patients with prostate cancer is critically dependent upon the stage of disease and the ultimate goal for treatment. A major difficulty in follow-up in prostate cancer is the lack of data on outcome of various treatment modalities. Additionally, there is a lack of data on the use of treatment modalities early in the course of prostate cancer. Despite these limitations, there is a need to develop an approach to follow these patients pending further study. In this review, we critically assess the natural course of untreated prostate cancer, the complications of local therapy, and the controversy over early versus delayed hormonal therapy. As a result of this discussion, common themes emerge. Most patients diagnosed with prostate cancer die of causes other than prostate cancer such as cardiovascular disease and therefore require additional follow-up. Since patients experience local problems such as urinary obstruction more commonly than symptomatic metastatic disease, instruments to assess urinary symptoms are discussed. Finally, follow-up as a means to determine eligibility for clinical studies is discussed.

BMJ. 2002 Oct 5;325(7367):740. Related Articles, Links

Natural experiment examining impact of aggressive screening and treatment on prostate cancer mortality in two fixed cohorts from Seattle area and Connecticut.
Lu-Yao G, Albertsen PC, Stanford JL, Stukel TA, Walker-Corkery ES, Barry MJ.
HealthStat, Princeton, NJ 08543, USA.
OBJECTIVE: To determine whether the more intensive screening and treatment for prostate cancer in the Seattle-Puget Sound area in 1987-90 led to lower mortality from prostate cancer than in Connecticut. DESIGN: Natural experiment comparing two fixed cohorts from 1987 to 1997. SETTING: Seattle-Puget Sound and Connecticut surveillance, epidemiology, and end results areas. PARTICIPANTS: Population based cohorts of male Medicare beneficiaries aged 65-79 drawn from the Seattle (n=94 900) and Connecticut (n=120 621) areas. MAIN OUTCOME MEASURES: Rates of screening for prostate cancer, treatment with radical prostatectomy and external beam radiotherapy, and prostate cancer specific mortality. RESULTS: The prostate specific antigen testing rate in Seattle was 5.39 (95% confidence interval 4.76 to 6.11) times that of Connecticut, and the prostate biopsy rate was 2.20 (1.81 to 2.68) times that of Connecticut during 1987-90. The 10 year cumulative incidences of radical prostatectomy and external beam radiotherapy up to 1996 were 2.7% and 3.9% for Seattle cohort members compared with 0.5% and 3.1% for Connecticut cohort members. The adjusted rate ratio of prostate cancer mortality up to 1997 was 1.03 (0.95 to 1.11) in Seattle compared with Connecticut. CONCLUSION: More intensive screening for prostate cancer and treatment with radical prostatectomy and external beam radiotherapy among Medicare beneficiaries in the Seattle area than in the Connecticut area was not associated with lower prostate cancer specific mortality over 11 years of follow up.

Urology. 2001 Dec;58(6):977-82. Related Articles, Links

Treatments for prostate cancer in older men: 1984-1997.
Bubolz T, Wasson JH, Lu-Yao G, Barry MJ.
Dartmouth Medical School, Hanover, New Hampshire, USA

OBJECTIVES: To examine the temporal trends in radical prostatectomy (RP), brachytherapy (BT), and external beam radiotherapy (EBRT) rates among men aged 65 years or older for the period 1984 to 1997. METHODS: We used the retrospective population-based analysis of treatments for prostate cancer among Medicare beneficiaries. The rates of RP were obtained from Part A (hospital) Medicare data for 20% of the national sample for 1984 to 1997. The BT and EBRT rates for the period 1993 to 1997 were obtained from a 5% national sample of Physician/Supplier Part B data. The rates of treatment, 30-day mortality, and readmissions were included. RESULTS: The rate of RP peaked in 1992. From 1993 to 1997, its use decreased by 6% among men aged 65 to 69 years, 34% among men aged 70 to 74 years, and 50% for men aged 75 years or older. However, by 1997, the RP + BT treatment rate again approached the 1992 levels of RP alone; BT was used twice as often as RP in men aged 75 years or older. By 1997, the RP + BT + EBRT rate exceeded the 1993 rate for men aged 65 to 69 years and was again approaching the 1993 rate for men aged 70 to 74 years. From 1984 to 1997, the presence of comorbid conditions gradually declined for RP and accounted for more than 60% of the decrease in the short term mortality during this period. Variations in RP use by geographic region have also decreased. CONCLUSIONS: RP is now more selectively targeted for treatment of prostate cancer in men older than 70 years than in the past. However, since BT has been substituted for radical surgery in many of these older men, the total population-based treatment rates have changed very little over time.

J Urol. 2001 Sep;166(3):861-5. Related Articles, Links

Interval after prostate specific antigen testing and subsequent risk of incurable prostate cancer.

Yao SL, Lu-Yao G.
Merck Research Laboratories, Rahway, New Jersey, USA.

PURPOSE: Studies of the potential effect of prostate specific antigen (PSA) screening on a less than yearly basis have been limited to computer simulations using relatively small sample sets. Primary clinical data on this relationship have not been generally available. We examined the relationship of less frequent testing and the risk of nonlocalized incurable cancer. The effect of testing frequency on the risk of prostate biopsy in men ultimately diagnosed with cancer was also assessed. MATERIALS AND METHODS: The study included a population based sample of 36,422 men 65 years old or older residing in 9 geographic areas with newly diagnosed prostate cancer during 1989 to 1993. The primary end point was the risk of nonlocalized cancer, as determined by logistic regression. Patient age, geographic region, year of diagnosis and race were included as covariates. RESULTS: In men who would be diagnosed with prostate cancer the risk of nonlocalized cancer did not differ in those tested 2 or 3 years compared with the risk in those tested 1 year before diagnosis (relative risk 1.00, 95% confidence interval 0.84 to 1.20 and 1.02, 95% confidence interval 0.74 to 1.41, respectively). However, the risk of prostate biopsy in these men was directly related to the number of PSA tests performed (test for trend p = 0.0061). CONCLUSIONS: Patients who choose to undergo PSA testing may be tested on a biennial instead of annual basis without an increased risks of nonlocalized cancer. Decreasing the frequency of PSA testing may lead to fewer prostate biopsies.

J Natl Cancer Inst. 1999 Nov 17;91(22):1950-6. Related Articles, Links

Comment in:
* J Natl Cancer Inst. 1999 Nov 17;91(22):1906-7.

Population-based study of relationships between hospital volume of prostatectomies, patient outcomes, and length of hospital stay.

Yao SL, Lu-Yao G.
S.-L. Yao, Merck Research Laboratories, Rahway, NJ 07065-0900, USA. siulong_yao@merck.com

BACKGROUND: Despite the large number of prostatectomies performed annually, few data exist regarding relationships between the volume of prostatectomies handled by a hospital, the length of a patient's stay in the hospital, and patient outcomes. We examined the effect of hospital prostatectomy volume and changes in the hospital volume on patient outcomes and the length of a patient's stay. METHODS: We collected data on 101

604 prostatectomies from Medicare claims filed from 1991 through 1994. By use of logistic regression and analysis of variance, we examined relationships between hospital load of prostatectomies, length of a patient's hospital stay, surgical complications, readmission rate, and mortality rate in a 30-day period following surgery. Statistical tests were two-sided. RESULTS and CONCLUSIONS: Cross-sectional analyses revealed that, compared with high-volume hospitals, low-volume, medium-low-volume, and medium-high-volume hospitals had higher relative risks of readmission by 30% (95% confidence interval [CI] = 21%-39%), 16% (95% CI = 7%-25%), and 8% (95% CI = -1% to 17%), respectively; higher relative risks of serious complications by 43% (95% CI = 37%-48%), 25% (95% CI = 19%-31%), and 9% (95% CI = 3%-15%), respectively; and higher relative risks of mortality by 51% (95% CI = 25%-77%), 43% (95% CI = 17%-69%), and 42% (95% CI = 16%-68%), respectively. The mean length of a patient's stay in a low-volume hospital was 9% longer than that in a high-volume hospital (8.51 days [95% CI = 8.47-8.56] versus 7.81 days [95% CI = 7.77-7.85]; P for trend across all volume categories =.0001). Within-hospital longitudinal analyses revealed that hospitals with a relative increase in prostatectomy volume had a 57% greater reduction in the length of a patient's stay compared with those with a relative decrease in volume (P =.005). Changes in prostatectomy volume did not affect the frequency of complications, mortality, and readmission. These findings suggest that an increase in a given hospital's prostatectomy volume may facilitate a decrease in the length of a patient's stay without an adverse impact on patient outcomes.

Urology. 1999 Aug;54(2):301-7. Related Articles, Links

Effect of age and surgical approach on complications and short-term mortality after radical prostatectomy--a population-based study.

Lu-Yao GL, Albertsen P, Warren J, Yao SL.
HealthStat, Princeton, New Jersey, USA.

OBJECTIVES: To use population-based data to accurately delineate the types and incidence of complications, risk of readmission, and influence of age and surgical approach on short-term mortality after radical prostatectomy. METHODS: Medicare claims from 1991 to 1994 were used to identify and quantify the types and risks of complications, rehospitalization within 90 days, and mortality at 30 and 90 days after perineal or retropubic prostatectomy. Logistic regression was used to determine the relationships between age, surgical approach, and short-term outcomes while adjusting for potential confounders. RESULTS: On the basis of data from 101,604 men, complications affected 25.0% to 28.8% of patients treated with the perineal or retropubic approach. The retropubic approach had a higher risk of respiratory complications (relative risk [RR] = 1.53, 95% confidence interval [CI] 1.37 to 1.71) and miscellaneous medical complications (RR = 1.77, 95% CI 1.60 to 1.97) and a lower risk of miscellaneous surgical complications (RR = 0.86, 95% CI 0.78 to 0.94). Differences in medically related gastrointestinal complications partially accounted for the differences in miscellaneous medical complications. Rectal injury with the perineal approach was only approximately 1% to 2%. Readmission within 90 days was necessary for 8.5% to 8.7% of patients who underwent the retropubic or perineal approach. The 30-day mortality was less than 0.5% for men aged 65 to 69; it approached 1% for men aged 75 and older. CONCLUSIONS: Complications and readmission after prostatectomy are substantially more common than previously recognized. Notable differences exist in the incidence of respiratory and nonsurgical gastrointestinal complications, although many short-term outcomes are comparable for the two approaches. Older age is associated with elevated surgical mortality and complications.

Lancet. 1997 Mar 29;349(9056):906-10. Related Articles, Links

Comment in:

* Lancet. 1997 Mar 29;349(9056):892-3.
* Lancet. 1997 May 24;349(9064):1551; author reply 1551-2.

Population-based study of long-term survival in patients with clinically localised prostate cancer.

Lu-Yao GL, Yao SL.
Health Care Financing Administration, Office of Research and Demonstrations, Baltimore, MD 21244-1850, USA.
BACKGROUND: Choice of treatment in localised prostate cancer has been hampered by a lack of unbiased, representative data on outcome. Most existing data have come from small cohorts at specialised academic centres; precise overall and cancer-grade-specific data are not available, and the data are subject to differential staging bias. Randomised clinical trials have been undertaken, but the results will not be available for another decade. We have carried out a large population-based study to ascertain overall and prostate-cancer-specific survival in men treated by prostatectomy, radiotherapy, or conservative management. METHODS: Data for 59,876 cancer-registry patients aged 50-79 were analysed. We examined the effect of differential staging of prostate cancer by analysing the data both by intention to treat and by treatment received. Estimated survival was calculated by the Kaplan-Meier method. FINDINGS: By the intention-to-treat approach, 10-year prostate-cancer-specific survival for grade 1 cancer was 94% (95% CI 91-95) after prostatectomy, 90% (87-92) after radiotherapy, and 93% (91-94) after conservative management. The corresponding survival figures in grade 2 cancers were 87% (85-89), 76% (72-79), and 77% (74-80); those in grade 3 cancer were 67% (62-71), 53% (47-58), and 45% (40-51). Although the intention-to-treat and treatment-received analyses yielded similar results for radiotherapy and conservative management, the 10-year disease-specific survival after prostatectomy differed substantially (83% [81-84] by intention to treat vs 89% [87-91] by treatment received). INTERPRETATION: The overall and cancer-grade-specific survival found in this study differ substantially from those in previous studies. Previous studies that used a treatment-received approach have generally overestimated the benefits of radical prostatectomy. We found that grade 3 tumours are highly aggressive irrespective of stage.
PMID: 9093251 [PubMed - indexed for MEDLINE]

In vitro trial of the pilot prototype of the prostate mechanical imaging system.
Weiss RE, Hartanto V, Perrotti M, Cummings KB, Bykanov AN, Egorov V, Sobolevsky SA.
Division of Urology, Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA.
OBJECTIVES: To compare the sensitivity and accuracy of the mechanical imaging system (MI system) to that of the simulated digital rectal examination (DRE) in detecting nodules within fabricated rubber prostate phantoms. Mechanical imaging is a new technology for visualizing and characterizing tissues using mechanical strain and stress data. METHODS: Twelve rubber phantoms were designed to simulate human prostates. Ten phantoms contained hard nodules in various locations. Two phantoms contained no nodules. Each model was examined with the MI system by a urologist (R.E.W.) and research student. Three-dimensional images of the examined prostate phantoms with and without nodules were generated by the MI system software. Blind DRE was performed on each phantom independently by the urologist and student. The results of the MI examinations and DREs were compared for sensitivity in detecting the presence and location of nodules within the prostate phantoms. RESULTS: Three-dimensional MI images reconstructed from both the student and the urologist examination data demonstrated 100% of the nodules in the appropriate locations. The DREs by the urologist detected 83% of the nodules in the appropriate locations. The DREs by the student detected 67% of the nodules in the appropriate locations. CONCLUSIONS: The prostate MI system allowed the detection of nodules in the prostate phantoms with sensitivity exceeding that of an experienced urologist. In contrast to the DRE, the results of the MI examination appear to be independent of the operator's experience. Therefore, the MI system is a promising means of accurate, sensitive, objective, and recordable detection of hard nodules within the prostate.

Cancer Metastasis Rev. 2003 Mar;22(1):83-6. Related Articles, Links

Prostate cancer in black and white Americans.
Reddy S, Shapiro M, Morton R Jr, Brawley OW.
Winship Cancer Institute, Emory University, Atlanta, Georgia, USA. kanthi_reddy@hotmail.com
The prostate cancer incidence and mortality of black Americans is among the highest in the world. The reasons have not been adequately explained. Similar disparities have been noted for men of sub-Saharan origin living in Brazil and the Caribbean. Avenues of investigation have assessed racial and ethnic differences in diet as well as

possible differences in the prevalence of genetics (both polymorphisms and mutations). There are studies to suggest that there are no racial differences in outcome when there is equal treatment. Several studies show that there are racial differences in patterns of care in the US and it has been hypothesized that this contributes to some of the racial disparity in survival after diagnosis.\

Grace Liu Yao///George Rhodes
Delivery of toxic agents to prostate cancer cells.
Multiple investigators have interest in the delivery of agents specifically to prostate cancer cells. **Monica Roth's** group has been developing novel method to screen for the productive entry of retroviruses into selective cell types utilizing novel receptor proteins. The approach utilizes a retroviral Env random display library, in which the limited receptor binding region of the FeLV A virus has been randomized. They have used this random Env library to screen for novel isolates which specifically infect prostate cells. They have isolated novel Env isolates that infect PC-3 prostate cell lines under conditions that the parental virus is non-infectious. Their goal is to develop these new Env proteins to deliver toxic compounds and/or genes into prostate tumors.

Dr. DiPaolaDiPaola has studied the effect of a PSA activated doxorubicin peptide conjugate in patients with HORMONE REFRACTORY PROSTATE CANCER (See table 1). **Dr. Hu** is interested in the study of other conjugated agents in hormone refractory prostate cancer and was recently the recipient of our prostate center pilot project award. **(Need more Hu data)**.

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Appendix I

Program for Workshop I: The Disease and the Dilemma: A Workshop on Prostate Cancer
Saturday, October 9, 1999
Keynote Address:
Leland Chung, Ph.D. "Translating basic research into clinical trials"

Educational lectures:

Michael M. Shen, Ph.D	"Prostate Development and Its Relationship to Carcinoma"
Cory Abate-Shen, Ph.D.	"Molecular Biology of the Normal and Abnormal Prostate"
Michael A. Gallo, Ph.D.	"Hormonal Mechanisms of Prostate Carcinogenesis"
Kenneth B. Cummings, M.D.	"Prostate Cancer: A Urologists Perspective"
Robert DiPaola, M.D.	"Clinical Approaches to Treating Prostate Cancer"

Program for Workshop I: Prostate Cancer Center Scientific Retreat
Saturday, December 8, 2001

Robert DiPaola Translational Research in Prostate Cancer
Tamara MinkoEnhancing the Efficacy of Chemotherapeutic Drugs by the Suppression of Antiapoptotic Cellular Defense
Steve Marcella PSA Screening and Prostate Cancer Mortality: Preliminary Evidence of Increased Incidence of Prostatism in Clinically Aggressive Prostate Cancer
Carlos Molina Regulation of the Transcriptional Repressor cAMP Early Repressor in Prostate Cancer Cells
Keith Bupp Targeting Retrovirus Using random Display envelop libraries
Stuart Lutzker Abrogation of the Mitotic Spindle-checkpoint in Prostate Cancer Cells and Sensitivity to Antimicorotubule Drugs
John Pintar Prostate Abnormalities in IGFBP KO Mice
Arnold Rabson Mechanisms of Constitutive NF-*k*B Activation in Human Prostate Cancer Cells
Bill Hait Molecular Determinants of Response to Therapy in Patients with Prostate Cancer
Zui Pan Ca2+ Signaling and Bax Translocation in Apoptosis of Prostate Cancer Cell Lines

Michael Shen Roles for Nkx3.1 in prostate development and cancer
Cory Abate-Shen Cooperativity of Tissue-Specific and Broad-Spectrum Tumor Suppressor Genes in a Mouse Model of Prostate Cancer

Symposium: *Prostate Cancer Symposium*
April 24, 2002

Plenary Presentations:

Gerald R. Cunha, Ph.D.	"Tissue recombinant models of prostatic carcinogenesis"
Philip Kantoff, M.D.	"Clinical progress in prostate cancer"
Angelo DeMarzo, M.D., Ph.D.	"Prostate cancer: Precursors and pathobiology"

ADD – program for Dec. 11th

Workshop: Program Project Pre-review

Simon Cherry — *Technologies for In Vivo Imaging of Mouse Models of Cancer*
Danny Reinberg — Project 1 – *Ezh2 and associated proteins in prostate cancer*
Michael Shen — Project 2 — *Analysis of metastatic disease in mouse models of prostate cancer*
Cory Abate-Shen — Project 3 — *Modeling hormone refractory prostate cancer in the mouse*
Joe Fondell — Project 4 — *Analysis of AR-interacting proteins and their roles in hormone-dependent and independent transcriptional regulation*
Simon Cherry — *Pathology and Imaging Core*
Michael Shen — *Mouse Knock-out Core*
Cory Abate-Shen — *Prostate Technologies Core*

Pilot grant programs and fellowships:
This grant program was implemented to encourage investigators to initiate new research projects in prostate cancer. Grant awards included the following:

K.V. Chin	"Profiling Gene Expression Patterns in Prostate Cancer
Stuart Lutzker	"Abrogation of the mitotic spindle-checkpoint in prostate cancer cells"
John Pintar	"Genetic studies of IGFBP function during prostate tumorigenesis"
Arnold Rabson	"Role of NF-kB in Prostate Cancer"
Robert Weiss	"Presence of green tea in the prostate"
Longqin Hu	"Alkylating agents to target site-specifically slow-growing prostate cancer cells"
Allan Conney	"Effect of 12-0-tetradecanoylphorbol-13-acetate (TPA) on prostate growth"
Carlos Molina	"Regulation of the putative tumor suppressor ICEr in prostate cancer by PTEN"

***** we need to add the outcomes!! Grants and publications!!!**

In addition to these studies members of the prostate program are developing novel strategies for chemotherapy. For example, **Dr. Lonqin Hu** has been utilizing synthetic medicinal chemistry and bioorganic chemistry to design anticancer prodrugs that target these enzymes in advanced prostate cancer. Currently, they are targeting signaling pathways that are utilized by protein serine/threonine kinases. They have designed a series of prodrugs that are activated site-specifically in tumor tissues. Their approach utilizes mechanism and inhibition of enzyme action to target the relevant pathways.

J Med Chem. 2003 Nov 6;46(23):4818-21. Related Articles, Links

Nitroaryl phosphoramides as novel prodrugs for E. coli nitroreductase activation in enzyme prodrug therapy.

Hu L, Yu C, Jiang Y, Han J, Li Z, Browne P, Race PR, Knox RJ, Searle PF, Hyde EI.

Department of Pharmaceutical Chemistry, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, 160 Frelinghuysen Road, Piscataway, New Jersey 08854, USA.

Cyclic and acyclic nitroaryl phosphoramide mustard analogues were activated by E. coli nitroreductase, an enzyme explored in GDEPT. The more active acyclic 4-nitrobenzyl phosphoramide mustard (7) showed 167 500x selective cytotoxicity toward nitroreductase-expressing V79 cells with an IC(50) as low as 0.4 nM. This is about 100x more active and 27x more selective than CB1954 (1). The superior activity was attributed to its better substrate activity (k(cat)/K(m) 19x better than 1) and/or excellent cytotoxicity of phosphoramide mustard released. Bioorg Med Chem. 2003 Sep 15;11(19):4171-8. Related Articles, Links

Nitrobenzocyclophosphamides as potential prodrugs for bioreductive activation: synthesis, stability, enzymatic reduction, and antiproliferative activity in cell culture.

Li Z, Han J, Jiang Y, Browne P, Knox RJ, Hu L.

Department of Pharmaceutical Chemistry, Ernest Mario School of Pharmacy, Rutgers, the State University of New Jersey, 160 Frelinghuysen Road, Piscataway, NJ 08854, USA.

In efforts to obtain potential anticancer prodrugs for gene-directed enzyme prodrug therapy using Eschericia coli nitroreductase, a series of four benzocyclophosphamide analogues were designed and synthesized incorporating a strategically placed nitro group in a position para to the benzylic carbon for reductive activation. All four analogues were found to be stable in phosphate buffer at pH 7.4 and 37 degrees C and were good substrates of E. coli nitroreductase with half lives between 7 and 24 min at pH 7.0 and 37 degrees C. However, only two analogues 6a and 6c, both with a benzylic oxygen in the phosphorinane ring para to the nitro group, showed a modest 33-36-fold enhanced cytotoxicity in E. coli nitroreductase-expressing cells. These results suggest that good substrate activity and the para benzylic oxygen are required for activation by E. coli nitroreductase. Compounds 6a and 6c represent a new structure type for reductive activation and a lead for further modification in the development of better analogues with improved selective toxicity to be used in gene-directed enzyme prodrug therapy.

Bioorg Med Chem. 2003 Sep 1;11(18):3889-99. Related Articles, Links

5'-(2-Nitrophenylalkanoyl)-2'-deoxy-5-fluorouridines as potential prodrugs of FUDR for reductive activation.

Liu B, Hu L.

Department of Pharmaceutical Chemistry, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, 160 Frelinghuysen Road, Piscataway, NJ 08854, USA.

Four 5'-(2-nitrophenylalkanoyl)-2'-deoxy-5-fluorouridines (1a-d) were designed and synthesized as potential prodrugs of FUDR for reductive activation. Two methyl groups were introduced alpha to the ester carbonyl to increase both the rate of cyclization activation and the stability of the conjugates towards serum esterases. Chemical reduction of the nitro group into an amino leads to cyclization and release of the active FUDR. Kinetic analysis of the cyclization activation process indicates that the two methyl groups alpha to the ester carbonyl restrict the rotational freedom of ground state molecule and promote the cyclization reaction. However, the two methyl groups also were found to render the conjugates as poor substrates of E. coli B nitroreductase. Conjugate 1c, without the two methyl groups, was reduced by E. coli B nitroreductase (t(1/2)=8 h) to give two products, a N-hydroxyl lactam and the drug FUDR, suggesting that the enzymatic reduction and subsequent cyclization activation proceeded through the hydroxylamine intermediate. These results indicate that cyclization activation will occur once the nitro group is reduced either to an amino or to a hydroxylamino group. The fact that the amino intermediates cyclized easily to release the incorporated drug FUDR suggests the feasibility of using peptide-linked acyl 2-aminophenylalkanoic acid esters as potential prodrugs for proteolytic activation.

Bhatia-Guar, R. Donjacour, A.A., Sciavolino, P.J., Kim, M., Desai, N., Young, P., Norton, C., Gridley, T., Cardiff, R.D., Cunha, G.R., Abate-Shen, C. and Shen, M.M. (1999). Roles for *Nkx3.1* in prostate development and cancer. *Genes Dev.* 13:966-977.

Kim, M., Cardiff, R., Desai, N., Banach-Petrosky, W., Parsons, R., Shen, M. and Abate-Shen, C. (2002). Cooperativity of *Nkx3.1* and *Pten* loss-of-function in a mouse model of prostate carcinogenesis. *Proc. Natl. Acad. Sci. USA* 99:2884-2889.

Kim, M., Bhatia-Gaur, R., Banach-Petrosky, W., Desai, N., Wang, Y., Hayward, S., Cunha, G., Cardiff, R., Shen, M. and Abate-Shen, C. (2002). *Nkx3.1* mutant mice recapitulate early stages of prostate carcinogenesis. *Cancer Research* 62:2999-3004.

Park, J.H., Walls, J.E., Galvez, J.J., Kim, M., Abate-Shen, C., Shen, M. and Cardiff, R.D. (2002). Prostatic Intraepithelial Neoplasia In Genetically Engineered Mice. *Am. J. Path.* 161:727-735

Abate-Shen, C. and Shen, M. (2000). Molecular genetics of prostate cancer. *Genes Dev.* 14:2410-2434.

Abate-Shen, C. and Shen, M.M. (2002). Mouse models of prostate carcinogenesis. Trends Genet. 18, (5) S1-S5 (online).

Abate-Shen, C. (2002). Deregulated homeobox gene expression in cancer: cause or consequence? *Nature Reviews Cancer* 2:777-85.

Kim, M., Bhatia-Gaur, R., Desai, N., Cardiff, R.D., Shen, M.M. and Abate-Shen, C. (2000). Mouse models of prostate cancer based on *NKX3.1* mutant mice. American Association for Cancer Research, Annual Meeting, San Francisco, CA.

Abate-Shen, C., Kim, M., Desai, N., Banach-Petrosky, W., Cardiff, R. and Shen, M.M. (2002). Mouse models of prostate cancer initiation and progression. American Association for Cancer Research, Annual Meeting, San Francisco, CA.

Abate-Shen, C., Kim, M., Ouyang, X., Gao, H., Banach-Petrosky, W., Sun, X., Cardiff, R. and Shen, M.M. (2002). Mouse models of prostate cancer initiation and progression. Cold Spring Harbor Meeting on Mouse Molecular Genetics, Cold Spring Harbor, NY.

Dr. Cory Abate Shen Presentations:

1999 US-Japan Program Workshop on Developmental Regulators and Cancer, Maui HI

NIH, Departments of Urology and Pathology, Bethesda MD

Distinguished Lecture Series, Wistar Institute, PA

U.C. Davis Cancer Center Seminar Series, Davis, CA

2000 American Association for Cancer Research Special Conference, Transcription Factor Pathogenesis of Cancer at the Millennium, Dana Point CA

Jonsson Cancer Comprehensive Center, Prostate Cancer Seminar Series, University of California, Los Angeles CA

MD Anderson Cancer Center, University of Texas, Houston TX

Max Delbruck Center for Molecular Medicine, Berlin, Germany

German Cancer Research Center, Heidelberg, Germany

Mouse Models of Human Cancer Consortium, Chantilly, VA

SPORE grant program Annual Meeting, Chantilly, VA

Pre-clinical Models in Prostate Cancer Research, Houston, TX

2001 Symposium Organizer, Annual Meeting of the American Association for Cancer Research, New Orleans, LA

NCI/Mouse Models of Human Cancer Consortium Satellite Meeting on PreClinical Trials, Bethesda MD

Skirball Institute, New York University, New York, NY

MD Anderson Cancer Center, University of Texas, Houston, TX

Mouse Models of Human Cancer Consortium Steering Committee Meeting, San Francisco, CA

UCSF Mini-Symposium on Mouse Models of Angiogenesis, San Francisco, CA

Meeting Organizer, Mouse Models of Prostate Cancer, Bar Harbor, MI

2002 Huntsman Cancer Institute at the University of Utah, Salt Lake City, Utah

Mouse Models of Human Cancer Consortium Steering Committee Meeting, Boston, MA

Chair and Invited Speaker, Cold Spring Harbor Meeting on Mouse Molecular Genetics, Cold Spring Harbor, NY

9th Prouts Neck Meeting on Prostate Cancer, Prouts Neck, ME

First Joint Meeting of the Mouse Models of Human Cancers Consortium (MMHCC) and the Prostate SPOREs, Bethesda, MD

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DiPaola R.S., Aisner J. Overcoming bcl-2 and p53 mediated resistance in Prostate Cancer. Seminars of Oncology, 26: 112-116, 1999.

DiPaola R.S., Rafi M., Vyas V., Gupta E., Toppmeyer D., Rubin Eric, Patel G., Goodin S., Medina P., Zamek R., Zhang C., White E., Hait W.N. Phase I clinical and pharmacologic study of 13-cis retinoic acid, alpha interferon and paclitaxel in patients with prostate cancer and other advanced malignancies. J Clin Oncol 17:2213-2218, 1999.

DiPaola, R.S. Approaches to the treatment of patients with hormone sensitive prostate cancer. Seminars of Oncology 26:24-27, 1999.

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Cvijic M.E., Kita T., Shih W., DiPaola R.S., and Chin K.V. Extracellular Catalytic Subunit Activity of the cAMP-Dependent Protein Kinase in Prostate Cancer. Clin Cancer Research, 2000.

Rafi M.M., Rosen R.T., Vassil A., Ho C., Zhang H., Ghai G., Lambert G., Hait W.N., DiPaola R.S. Modulation of bcl-2 and Cytotoxicity by Licochalcone-A, a novel estrogenic flavonoid. Anticancer Research, 20:2653-2658, 2000.

Goodin S., DiPaola RS. Is there science for alternative medicine in prostate cancer? Highlights in Oncology Practice 18(3):72-76, 2000.

DiPaola R.S., P. Kumar, W.N. Hait, and R. Weiss. State of the Art Treatment and research in Prostate Cancer. New Jersey Medicine, 2:23-34, 2001.

Nanquan Zhu, Rafi M.M., DiPaola R.S., Jingsong Xin, Chee-kok Chin, Vladimir Badmaev, Geetha Ghai, Rosen R., Chi-Tang Ho. Bioactive constituents from Gum Guggul (Commiphora wiightii). Phytochemistry 56:723-727, 2001.

Eid J.E., Brunner M., Segal L., Cummings K.B., Weiss R.E., Goodin S., Todd M., Aisner J., DiPaola R.S. Effect of P-30 Protein and Tamoxifen on TGF-Beta1 and IGF-1 in Patients with Prostate Cancer, Urologic Oncology 6:243-247, 2001.

DiPaola RS, Chenven ES, Shih WJ, Lin Y, Amenta P, Goodin S, Shumate A, Rafi MM, Capanna T, Cardiella M, Cummings KB, Aisner J., Todd M. Mitoxantrone in patients with prostate specific antigen progression after local therapy for prostate cancer. Cancer. 2001 Oct 15;92(8):2065-71.

DiPaola R.S., Patel J., Rafi M.M. Targeting Apoptosis in Prostate Cancer. Hematology/Oncology Clinics of North America. 15:3:509-524, 2001.

Zhu Nanqun, Kikuzaki H, Sheng S, Rafi MM, Nakatani N, DiPaola RS, Ghai G, Rosen R, Ho CT. Furanosesquiterpenoids of Commiphora Myrrh. J Nat Prod. 2001 Nov;64(11):1460-2.

Rafi MM, Vastano BC, Ho C-T, Ghai G, Rosen RT, and DiPaola RS. Novel polyphenol molecule isolated from licorice root (glycrrhiza glabra) induces apoptosis, G2/M cell cycle arrest, and bcl-2 phosphorylation in tumor cell lines. J. Agric and Food Chemistry 50:677-684, 2002.

DiPaola RS, Rinehart J, Nemunaiti J, Effinghaus S, Rubin E, Capanna T, Ciardella M, Fontaine M, Adams N, Williams A, Schwartz M, Winchell G, Wickersham K, Deutsch P, Yao S. Characterization of a novel prostate specific antigen activated peptide-doxorubicin conjugate in patients with prostate cancer. J Clin Oncol. 2002 Apr 1;20(7):1874-1879.

Morris M, Tong WP, Cordon-Cardo C, Drobnjak M, Kelly WK, Slovin S, Terry KL, DiPaola RS, Rafi MM, Rosen N, Scher HI. A phase I trial of G3139, a bcl-2 antisense drug, by continuous infusion as a single agent and with weekly taxol Clin Cancer Res. 2002 Mar;8(3):679-83.

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S. Goodin, K. Rao, and R.S. DiPaola. State of the Art Therapies in Prostate Cancer. Oncologist 360-70, 2002.

Marks L, DiPaola R, Nelson P et al. PC-SPES: herbal formulation for prostate cancer. Urology 369-70, 2002.

DiPaola RS. To Arrest or not G2-M cell cycle arrest. The Biology Behind. Clin Cancer Res, 3311-4, 2002.

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Dr. Robert S. DiPaola Presentations:

1999

NOVEL THERAPIES IN CANCER OF THE PROSTATE:TARGETING BCL-2, Cancer Center Grand Rounds, University of Pennsylvania, Philadelphia PA, 1/99.

NOVEL THERAPY FOR PROSTATE CANCER, Seminar, University of Oklahoma, 2/99.

MODULATION OF PACLITAXEL CHEMOTHERAPY, Combined Medical and Radiation Oncology Grand Rounds, New York University, 3/17/99.

A UNIQUE PERSPECTIVE IN THE TREATMENT OF PATIENTS WITH HORMONE SENSITIVE PROSTATE CANCER, Univ of Chicago, taxotere seminar,4/27/99

PROSTATE CANCER, Grand Rounds, St.Vincent's Hospital, Staten Island, 5/6/99

NOVEL THERAPIES FOR PROSTATE CANCER, Oncology Grand Rounds, St. Elizabeth Hospital. NJ, 5/13/99

WEEKLY TAXOL/RETINOID/INTERFERON IN PROSTATE CANCER, MD Anderson W.I.S.E. conference, NY Palace Hotel, NY, 12/18/1999

2000

TAXOL/RETINOID/INTERFERON FOR HORMONE REFRACTORY PROSTATE CANCER, Fox Chase Investigators Meeting, Mandalay Bay, Lanai, 3/16/2000

THE ROLE OF CHEMOTHERAPY FOR PROSTATE CANCER, BMS Symposia, Las Vegas, 3/2000

ASCO UPDATE ON PROSTATE CANCER, BMS Symposia, Las Vegas Nevada, 6/30/2000

NOVEL THERAPY IN PROSTATE CANCER, Medical Oncology Symposia, Seattle WA. 8/10/2000

RETINOID, INTERFERON AND TAXOL RANDOMIZED AGAINST ESTRAMUSTINE, NAVELBINE, AND MITOXANTRONE, Glaxo Advisory Board, Denver CO, 8/25/2000

OVERVIEW OF PROSTATE CANCER, Distinguished lecture, Brookdale Medical Center, NY, 9/6/2000

AVENTIS ADVISORY BOARD MEETING, Lake Tahoe Nevada, 9//19/2000

NOVEL ESTROGENS IN PROSTATE CANCER, CAPCURE SYMPOSIA, Lake Tahoe Nevada, 9/24/2000

PROSTATE CANCER OVERVIEW, Medical Oncology Symposia, Intercontinental Hotel, Chicago, 10/6/2000

PC-SPES IN PROSTATE CANCER, THE AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO) SPECIAL SESSION LECTURE, Boston MA,10/23/2000

2001

UPDATE ON THERAPY FOR HRPC, Aventis advisory board, NY NY, 3/8/2001

AACR SESSION: PROSTATE CANCER OF MICE AND MEN: Chairman, New Orleans, LO 3/25/2001

TRANSLATIONAL APPROACHES IN PROSTATE CANCER, Oncology Grand Rounds at Dana Farber, Boston MA, 4/19/2001

A PSA ACTIVATED PRODRUG IN HRPC, MERCK ADVISORY BOARD, San Fran, CA, 5/11/2001

EFFECT OF ESTROGENS IN PROSTATE CANCER, Symposia on Genes and the Environment, NATIONAL ACADEMY OF SCIENCES, Washington DC, 5/17/2001

PC-SPES and prostate cancer, NATIONAL PROSTATE SYMPOSIA (NMCR): WASHINGTON DC, 5/26/2001

Treatment for stage D2 prostate cancer, NATIONAL PROSTATE SYMPOSIA (NMCR): Marriott Eastside NY, NY, 7/28/2001

Chairman of session and lecture on Estrogens and Prostate cancer, GORDON CONFERENCE, NH, 7/8/2001

State of the art treatment of hormone refractory prostate cancer, MAYO CLINIC SYMPOSIA, Amelia Island, FL 8/16/2001

Treatment for stage D2 prostate cancer, NATIONAL PROSTATE SYMPOSIA (NMCR): CHICAGO, 8/25/2001

Phytoestrogens in prostate cancer, CAPCURE Lecture, Lake Tahoe, 9/9/2001.

Lecture "Hormone refractory prostate cancer", NMCR Prostate Symposia, Dallas TX, 9/292001

Lecture on chemotherapy in prostate cancer. NMCR prostate symposia, Vegas, 11/3/2001

AMERICAN SOCIETY OF RADIATION ONCOLOGY (ASTRO), Special lecture. Complimentary medicine in Prostate cancer, 11/6/2001.

2002

NOCR SYMPOSIA ON PROSTATE CANCER, Atlanta Georgia, 2/12/2002.

ONCOLOGY SYMPOSIA ON BLADDER AND PROSTATE CANCER, Las Vegas NV, 2/24/2002

CYTOTOXIC CHEMOTHERAPY IN HRPC, Biltmore, Miami, 3/23/2002.

NOVEL APPROACHES IN PROSTATE CANCER: Medical Grand Rounds at Graduate Hospital, Philadelphia, 5/8/2002.

Presentation on PSA VACCINIA/FOWLPOX VACCINE WITH AND WITHOUT G-CSF FOR PATIENTS WITHS STAGE D0 PROSTATE CANCER (ECOG 5800) at Therion Advisory Board meeting, Orlando FL, 5/17/2002.

NMCR SYMPOSIA ON PROSTATE CANCER, NY, NY, 6/14/02

ASCO HIGHLIGHTS IN GU ONCOLOGY, San Diego CA, 6/30/02

CYTOTOXIC THERAPY IN PROSTATE CANCER, IPCME, St Petersburg FL, 7/12/02

PROSTATE SYMPOSIA, NMCR, Inverness CO, 7/26/02

NCI PSA VACCINE WORKING GROUP, Bethesda MD, 7/19

NCI WORKING GROUP ON RESEARCH WITH PC-SPES, Bethesda MD, 8/12/02

2003

AVENTIS ADVISORY BOARD, Prostate Cancer and Bcl-2, 1/03

MONTEFIORE SYMPOSIA LECTURE ON PROSTATE CANCER, NY, 6/03

TRANSLATIONAL RESEARCH IN PROSTATE CANCER: Jefferson Medical Center, Urology distinguished Lecture 2/03.

PROSTATE CANCER THERAPY: July, 18, 2003, Invited Speaker,. "ASCO highlights" Network for Medical Communication and Research, Las Vegas, NV.

December 18, 2003, Invited Speaker, "Amonafide Investigators Meeting", Chicago, IL.

OVERVIEW OF THERAPY FOR GU CANCER AT ASCO 2003. July 26, 2003, Invited Speaker, "ASCO highlights" Network for Medical Communication and Research, Hyatt Regency La Jolla, San Diego, CA.

ASCO 2003. August 9, 2003, Invited Speaker, "ASCO highlights Genitourinary Malignancy"Network for Medical Communication and Research, New York, NY.

August 25, 2003, Invited Speaker by NCI "Prostate Vaccine Program" Marriott Pookshill, Bethesda, Maryland.

September 19-20 2003, Invited Speaker, "Challenging Cases in Prostate Cancer"Network for Medical Communication and Research, Chicago, IL.

September 25, 2003 Grand Rounds, Invited Speaker, "High Risk prostate Cancer", Stony Brook University Hospital, Stonybrook NY.

October 3, 2003 Invited Speaker, MSKCC "ECOG Prostate Debate" – New York Westin Hotel, New York, NY.

October 4, 2003, Invited Speaker, "CTEP's studies of PROSTVAC and PANVAC", Therion Biologic, The Crowne Plaza Hotel, Times

2004

February 19-20, 2004, Invited Speaker "Genitourinary Cancer" 10th Annual Meeting, NMCR Educational Symposia, Las Vegas, NV.

FUTURE OF SYSTEMIC THERAPY IN PROSTATE CANCER: ASCO 2004 EDUCATIONAL SESSION, New Orleans.

July 2004. American College of Surgeons (ACOSOG), GU session "ECOG GU trials agenda", Chicago.

June 22-23, 2004, Invited Speaker, "ASCO review" - Columbus Community Clinical Oncology Program, Columbus, Ohio.

TRANSLATIONAL GU SYMPOSIA "GENITOURINARY MALIGNANCIES:BENCH, BEDSIDE, AND COOPERATIVE GROUPS" June 24-25, 2004, Invited Speaker, The University of Iowa College of Medicine, Iowa City, IA.

September 18, 2004. Invited Speaker, Future of Prostate Cancer: Urology/Medical oncology symposia on developing plans to increase Cooperative Group trial accrual. Four Seasons, Chicago.